STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 163072

TO: Rei-Tsang Shiao **Location: 5a10 / 5c18** **Saturday, August 20, 2005** **Art Unit: 1626** **Phone: 571-272-0707** **Serial Number: 10 / 688697**	**From: Jan Delaval** **Location: Biotech-Chem Library** **Remsen 1a51** **Phone: 571-272-2504** **jan.delaval@uspto.gov**

Search Notes

ACCESS DB # 163072

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Robert (Reb) Shiao Examiner #: 79521 Date: 8/19/05

Art Unit: 1626 Phone Number: 2-0907 Serial Number: 10/688,673

Location (Bldg/Room#): REM (Mailbox #): 4A18 / 5C78 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: new form for prepg losartan potassium

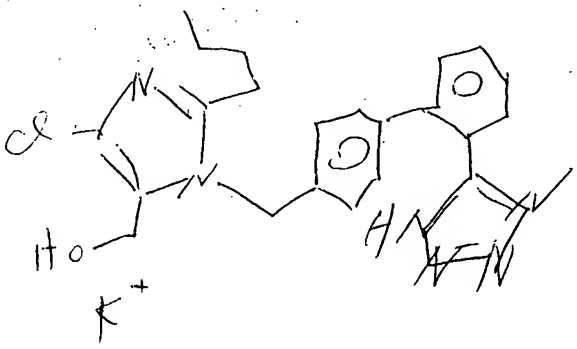
Inventors (please provide full names): Lifshitz et al

Earliest Priority Date: _____

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

I search losartan potassium (see claim 24)



II search pharmaceutical composition of losartan potassium, i.e. powder formulation, tablet

****

STAFF USE ONLY

Searcher: Jan

Searcher Phone #: 22504

Searcher Location: _____

Date Searcher Picked Up: 8/20/05

Date Completed: 8/20/05

Searcher Prep & Review Time: 16

Online Time: +40

Type of Search

____ NA Sequence (#)

____ AA Sequence (#)

____ Structure (#)

✓ Bibliographic

____ Litigation

____ Fulltext

____ Other

Vendors and cost where applicable

~~STN~~ ____ Dialog

____ Questel/Orbit ____ Lexis/Nexis

____ Westlaw ____ WWW/Internet

____ In-house sequence systems

____ Commercial ____ Oligomer ____ Score/Length

____ Interference ____ SPDI ____ Encode/Transl

____ Other (specify)

UNITED STATES PATENT AND TRADEMARK OFFICE

DATE: August 15, 2005

FROM: George Elliott, Bruce Kisliuk, Jasemine Chambers

TO: Technology Center 1600 Examiners and Managers

SUBJECT: Steps to Reduce STIC Search Backlogs

Because of the growing backlog and lengthening turnaround times of searches in STIC, we are asking that all examiners who request searches from STIC abide by the following guidelines.

- Rush searches should only be submitted when a search is needed to complete a date-sensitive action (amendment in danger of going overdue when the search could not have been submitted earlier, after final) in a timely fashion. Rush searches will not be approved without the reason for requesting Rush status being expressed.
- Searches should be as specific as reasonably possible. Vague searches or searches that say "see attached claims" will be returned to the examiner with a request for more specific information on what is needed. This has been the policy for some time—it will now be more strictly enforced.
- All search requests must be submitted to the front desk. Searches delivered directly to your favorite searcher will not be accepted. You will be asked to drop the search at the front desk.
- Indicate a realistic "date needed by" on the search request. Do not say that you need a search significantly before you actually expect to be working on the case for which that search is being ordered.
- Do not request sequence searches for cases that have failed to comply with the sequence rules, including submission of an acceptable CRF.

Thank you very much for your cooperation.

```
=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 09:29:28 ON 20 AUG 2005
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FILE COVERS 1907 - 20 Aug 2005  VOL 143 ISS 9
FILE LAST UPDATED: 19 Aug 2005  (20050819/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d l48 all hitstr tot

L48  ANSWER 1 OF 14  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:414643  HCAPLUS
DN   140:412339
ED   Entered STN:  21 May 2004
TI   Crystalline form of losartan potassium
IN   Reddy, Manne Satyanarayana; Eswaraiah, Sajja; Koppera, Ravinder Reddy;
     Reddy, Vajrala Venkata
PA   Reddy's Laboratories Limited, India; Reddy's Laboratories, Inc.
SO   U.S. Pat. Appl. Publ., 11 pp.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  A61K031-4178
     ICS  C07D043-02
INCL 514381000; 548254000
CC   63-6 (Pharmaceuticals)
     Section cross-reference(s): 28, 75
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     --------------      ----   --------    --------------------   --------
PI   US 2004097568        A1    20040520    US 2003-629316         20030729 <--
PRAI IN 2002-MA568        A     20020729  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 US 2004097568    ICM    A61K031-4178
                  ICS    C07D043-02
                  INCL   514381000; 548254000
 US 2004097568    NCL    514/381.000
                  ECLA   A61K031/4178; C07D403/10+257+233                <--
AB   A compound that is a crystalline Form III of losartan
     potassium is provided.  Also provided are compns. containing the
     compound and methods for its preparation  For example, 125 g of trityl
```

10/629316

losartan (preparation given) was mixed with an aqueous solution containing 11 g of KOH, 125 mL water, and 1250 mL methanol until the reaction was complete. The solvent was distilled off the reaction solution under vacuum, and water (325 mL) added to the residual mass, stirred for 30 min, the pH adjusted to 8.2 to 8.8, and the mass filtered. The filtrate was washed with water, the water was distilled off, and the resulting residue was dissolved in methanol, the solvent distilled off, and the residual mass cooled to a temperature of 5 to 10°, filtered, and dried to yield **crystalline** polymorph Form III of **losartan potassium** (weight 43.0 g). The **crystalline** polymorph Form III of **losartan potassium** was also obtained from **crystalline** polymorph Form I of **losartan potassium.**

ST **losartan potassium** polymorph prepn dosage form

IT Drug delivery systems
(liqs.; preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT Polymorphism (**crystal**)
(preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT Drug delivery systems
(solids; preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT Drug delivery systems
(topical; preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT **124750-99-8P, Losartan potassium**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of **crystalline** form of **losartan potassium** for dosage forms)

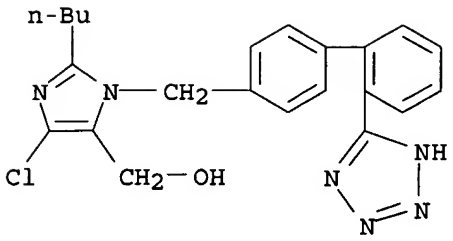
IT 83857-96-9 124750-51-2, N-(Triphenylmethyl)-5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT 124751-00-4P
RL: RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(preparation of **crystalline** form of **losartan potassium** for dosage forms)

IT **124750-99-8P, Losartan potassium**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of **crystalline** form of **losartan potassium** for dosage forms)

RN 124750-99-8 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



● K

L48 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:354789 HCAPLUS
DN 140:363006
ED Entered STN: 30 Apr 2004
TI Process for preparing **losartan potassium** with improved flowability
IN **Lifshitz, Igor; Kor, Ilan; Shabat, Shalom**
PA **Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceutical USA, Inc.**
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-4178
ICS A61K009-14
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004035049	A1	20040429	WO 2003-US32885	20031017 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004171843	A1	20040902	US 2003-688697	20031017 <--
	EP 1471908	A1	20041103	EP 2003-776442	20031017 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2002-419450P	P	20021017 <--		
	US 2002-426072P	P	20021112 <--		
	US 2002-426461P	P	20021114 <--		
	US 2002-431450P	P	20021204 <--		
	US 2002-431809P	P	20021209 <--		
	WO 2003-US32885	W	20031017		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES

WO 2004035049 ICM A61K031-4178
ICS A61K009-14
WO 2004035049 ECLA A61K031/4178; C07D403/10+257+233 <--
US 2004171843 NCL 548/254.000
ECLA A61K031/4178; C07D403/10+257+233 <--

AB Provided is a method of improving the flowability of **losartan potassium powder** having an initial Hausner ratio of 1.45 or more, which method includes re-slurrying the **losartan potassium** in a re-slurry solvent. Dry **losartan potassium** (50 g) was reslurried in **toluene** (200 mL) at about 25 °C for about 4 h. The suspension was filtered and dried under vacuum at about 50-60 °C for about 10 h. The Hausner ratio was decreased from about 1.50-1.60 to about 1.3-1.35. (yield = 98%).

ST process prepn **losartan potassium** improved flowability

IT Esters, uses
RL: NUU (Other use, unclassified); USES (Uses)
(alkyl; process for preparing **losartan potassium** with improved flowability)

IT Drug delivery systems
(**powders**; process for preparing **losartan potassium** with improved flowability)

IT Solvents
(process for preparing **losartan potassium** with improved flowability)

IT Alcohols, uses
Ethers, uses
Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for preparing **losartan potassium** with improved flowability)

IT Solvents
(protic; process for preparing **losartan potassium** with improved flowability)

IT **60-29-7, Diethyl ether**, uses 67-63-0, Isopropanol, uses **71-43-2, Benzene**, uses **108-87-2, Methylcyclohexane 108-88-3, Toluene**, uses **109-60-4, Propyl acetate 110-54-3, Hexane**, uses **110-82-7, Cyclohexane**, uses **123-86-4, Butyl acetate 141-78-6, Ethyl acetate**, uses **142-82-5, Heptane**, uses **142-96-1, Dibutyl ether 1330-20-7, Xylene**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for preparing **losartan potassium** with improved flowability)

IT **124750-99-8, Losartan potassium**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(process for preparing **losartan potassium** with improved flowability)

IT 1310-58-3, Potassium hydroxide, reactions 7647-01-0, Hydrochloric acid, reactions **114798-26-4, Losartan** 124751-00-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing **losartan potassium** with improved flowability)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

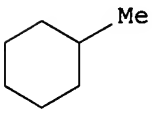
(1) Breen, P; US 5859258 A 1999 HCAPLUS
(2) Zion, D; WO 03048135 A 2003 HCAPLUS

IT **60-29-7, Diethyl ether**, uses **71-43-2**
, **Benzene**, uses **108-87-2, Methylcyclohexane**
108-88-3, Toluene, uses **109-60-4,**
Propyl acetate 110-54-3, Hexane,
uses **110-82-7, Cyclohexane**, uses **123-86-4,**
Butyl acetate 141-78-6, Ethyl
acetate, uses **142-82-5, Heptane**, uses
142-96-1, Dibutyl ether 1330-20-7,
Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for preparing **losartan potassium** with
improved flowability)
RN 60-29-7 HCAPLUS
CN Ethane, 1,1'-oxybis- (9CI) (CA INDEX NAME)

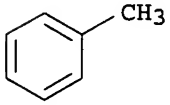
$H_3C-CH_2-O-CH_2-CH_3$

RN 71-43-2 HCAPLUS
CN Benzene (8CI, 9CI) (CA INDEX NAME)

RN 108-87-2 HCAPLUS
CN Cyclohexane, methyl- (8CI, 9CI) (CA INDEX NAME)



RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



RN 109-60-4 HCAPLUS
CN Acetic acid, propyl ester (6CI, 8CI, 9CI) (CA INDEX NAME)

n-Pr—O—Ac

RN 110-54-3 HCAPLUS
CN Hexane (8CI, 9CI) (CA INDEX NAME)

Me—$(CH_2)_4$—Me

RN 110-82-7 HCAPLUS
CN Cyclohexane (8CI, 9CI) (CA INDEX NAME)

RN 123-86-4 HCAPLUS
CN Acetic acid, butyl ester (8CI, 9CI) (CA INDEX NAME)

n-Bu—O—Ac

RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

RN 142-82-5 HCAPLUS
CN Heptane (8CI, 9CI) (CA INDEX NAME)

Me—$(CH_2)_5$—Me

RN 142-96-1 HCAPLUS
CN Butane, 1,1'-oxybis- (9CI) (CA INDEX NAME)

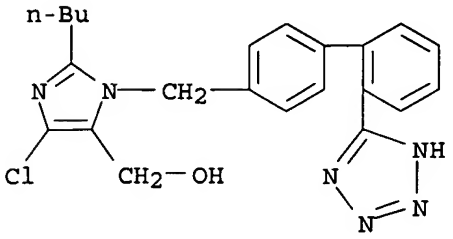
n-Bu—O—Bu-n

RN 1330-20-7 HCAPLUS
CN Benzene, dimethyl- (9CI) (CA INDEX NAME)

2 (D1—Me)

IT **124750-99-8, Losartan potassium**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(process for preparing **losartan potassium** with improved flowability)

RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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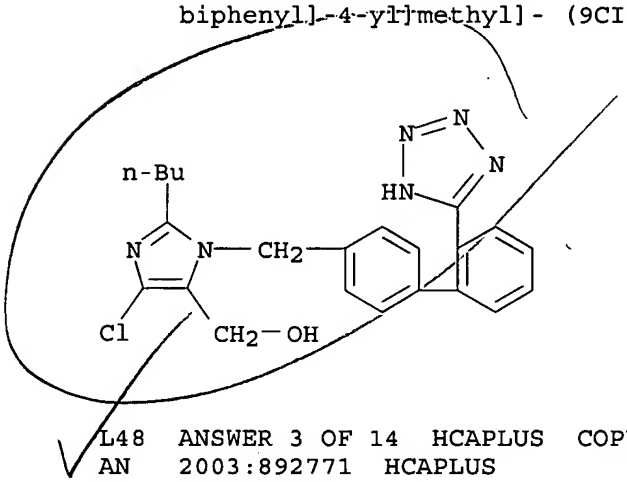
IT **114798-26-4, Losartan**
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for preparing **losartan potassium** with improved flowability)
RN 114798-26-4 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



L48 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:892771 HCAPLUS
DN 139:364939
ED Entered STN: 14 Nov 2003
TI Processes for preparing **losartan** by cleavage of triarylmethyl-substituted **losartans** in liquid ketones and **losartan potassium** by basification with potassium ions in pure liquid alcohols
IN Dolitzky, Ben-Zion
PA **Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceutical USA, Inc.**
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D401-10
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 45, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003093262	A2	20031113	WO 2003-US13369	20030429
	WO 2003093262	A3	20040318		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2482857	AA	20031113	CA 2003-2482857	20030429
	US 2004034077	A1	20040219	US 2003-426612	20030429
	EP 1474417	A2	20041110	EP 2003-726536	20030429
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2002-376322P	P	20020429		
	WO 2003-US13369	W	20030429		

10/426,612

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003093262	ICM	C07D401-10
WO 2003093262	ECLA	C07D403/10+257+233
US 2004034077	NCL	514/381.000
	ECLA	C07D403/10+257+233

OS MARPAT 139:364939

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention is directed to a process of preparation of the antihypertensive agent **losartan** (I) by acid-catalyzed cleavage of a triarylmethyl group from a triarylmethyl-substituted **losartans** II in a diluent comprising liquid ketone, basification, evaporation of the ketone, separation of the precipitated triarylmethanol from the residue, acidification of the remaining solution, and separation of the precipitated I [wherein R1, R2, R1', R2', R1'', R2'' = independently H, halo, NO2, CN, vinyl, styryl(un)substituted alkyl, alkenyl, COH and derivs., CO2H and derivs., OH and derivs., SH and derivs., NH2 and derivs., or R1CCR2, R1'CCR2', R1''CCR2'' = carbocyclyl, heterocyclyl, with one proviso]. The advantages include recyclability of the triarylmethanol recovered by precipitation from the residue in high yield (> 91%)and high purity (> 97%) in the preparation of I, and elimination of water distillation and addition of an anti-solvent in the preparation of I•K. The invention is also directed to a process for preparation of I•K by basification of I with potassium ions in substantially pure liquid alc. and precipitation of the potassium salt. For example, I was prepared by HCl-cleavage of trityl **losartan** in acetone at room temperature, basification with KOH, evaporation of acetone, removal of triphenylmethanol (94.6% pure by HPLC), and acidification with HCl.

ST **losartan** prepn acid cleavage triarylmethyltetrazolylbiphenylmeth

ylimidazolylmethanol ketone solvent; basification **losartan potassium** prepn alc solvent

IT Bond cleavage
(acid catalyzed-; processes for preparing **losartan** and **losartan potassium**)

IT Antihypertensives
Human
Neutralization
(processes for preparing **losartan** and **losartan potassium**)

IT 67-64-1, Acetone, uses 78-93-3, Methyl ethyl ketone, uses 108-10-1, Methyl isobutyl ketone
RL: NUU (Other use, unclassified); USES (Uses)
(diluent; processes for preparing **losartan** and **losartan potassium**)

IT **114798-26-4P, Losartan**
RL: **IMF (Industrial manufacture)**; RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(processes for preparing **losartan** and **losartan potassium**)

IT **124750-99-8P, Losartan Potassium**
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(processes for preparing **losartan** and **losartan potassium**)

IT 1310-58-3, Potassium hydroxide, reactions 3999-70-0, Potassium butoxide 6831-82-9, Potassium isopropoxide 14764-60-4, Potassium isobutoxide
RL: RCT (Reactant); RACT (Reactant or reagent)
(processes for preparing **losartan** and **losartan potassium**)

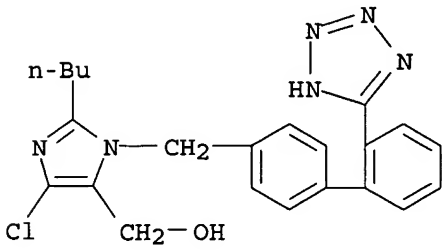
IT 76-84-6P, Triphenylmethanol
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(side product; processes for preparing **losartan** and **losartan potassium**)

IT 67-63-0, Isopropyl alcohol, uses 71-36-3, Butyl alcohol, uses 78-83-1, Isobutyl alcohol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; processes for preparing **losartan** and **losartan potassium**)

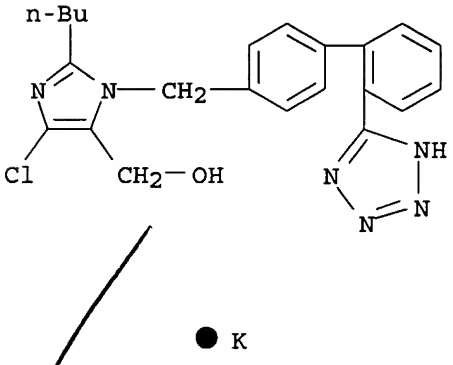
IT 133909-99-6, 2-Butyl-4-chloro-1-[[2'-(2-triphenylmethyl-2H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-31-1, 2-Butyl-4-chloro-1-[[2'-[2-[(p-methoxyphenyl)diphenylmethyl]-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-32-2, 2-Butyl-4-chloro-1-[[2'-[2-[di(p-methoxyphenyl)]phenylmethyl-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-33-3, 2-Butyl-4-chloro-1-[[2'-[2-tri(p-methoxyphenyl)methyl-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-34-4, 2-Butyl-4-chloro-1-[[2'-[2-[[(p-methoxyphenyl)(naphth-1-yl)]phenylmethyl]-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-35-5, 2-Butyl-4-chloro-1-[[2'-[2-[[(p-methoxyphenyl)(naphth-2-yl)]phenylmethyl]-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 622850-36-6, 2-Butyl-4-chloro-1-[[2'-[2-[di(p-methoxyphenyl)naphth-1-ylmethyl]-2H-tetrazol-5-yl][1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(triaryltetrazole reactant; processes for preparing **losartan** and **losartan potassium**)

IT **114798-26-4P, Losartan**

RL: **IMF (Industrial manufacture)**; RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(processes for preparing **losartan** and **losartan potassium**)
RN 114798-26-4 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



IT **124750-99-8P, Losartan Potassium**
RL: **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**
(processes for preparing **losartan** and **losartan potassium**)
RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



L48 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:454301 HCAPLUS
DN 139:26612
ED Entered STN: 13 Jun 2003
TI Amorphous and **crystalline** forms of **losartan potassium**
IN Dolitzky, Ben Zion; Weizel, Shlomit; Nisnevich, Gennady; Rukhman, Igor; Kaftanov, Julia
PA **Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceuticals USA, Inc.**
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent

LA English
IC ICM C07D257-04
ICS A61K031-41
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2003048135	A1	20030612	WO 2002-US36550	20021113	<--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	CA 2465597	AA	20030612	CA 2002-2465597	20021113	<--
	US 2004006237	A1	20040108	US 2002-293820	20021113	<--
	EP 1458693	A1	20040922	EP 2002-795637	20021113	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
PRAI	US 2001-333034P	P	20011114	<--		
	US 2002-401278P	P	20020805	<--		
	WO 2002-US36550	W	20021113	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2003048135	ICM	C07D257-04	
	ICS	A61K031-41	
WO 2003048135	ECLA	C07D403/10+257+233	<--
US 2004006237	NCL	548/257.000	
	ECLA	C07D403/10+257+233	<--

AB This invention relates to novel amorphous **losartan potassium**, novel **losartan potassium** in a **crystalline** form that is a hydrate, novel **crystalline losartan potassium** Form IV and solvates thereof, novel **crystalline losartan potassium** Form V and solvates thereof, to processes for their preparation, to compns. containing them and to their use in medicine. This invention further relates to a novel process for preparing **crystalline losartan potassium** Form I and Form II.

ST **losartan potassium** amorphous **crystal** form

IT **Crystal** morphology
(amorphous and **crystalline** forms of **losartan potassium**)

IT Alcohols, processes
RL: **PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)**
(amorphous and **crystalline** forms of **losartan potassium**)

IT Drug delivery systems
(capsules; amorphous and **crystalline** forms of **losartan potassium**)

IT Drug delivery systems
(oral; amorphous and **crystalline** forms of **losartan potassium**)

IT Drug delivery systems
(tablets; amorphous and **crystalline** forms of **losartan**

potassium)

IT **124750-99-8, Losartan potassium**
539820-64-9 539820-65-0 539820-66-1
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(amorphous and **crystalline** forms of **losartan potassium**)

IT 64-17-5, Ethanol, processes 67-56-1, Methanol, processes 67-63-0, Isopropanol, processes 67-64-1, Acetone, processes 75-05-8, Acetonitrile, processes 75-09-2, Methylene chloride, processes 78-93-3, Mek, processes **108-88-3, Toluene**, processes **110-54-3, Hexane**, processes **141-78-6, Ethyl acetate**, processes 616-38-6, Dimethyl carbonate 7732-18-5, Water, processes
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; **PROC (Process)**
(amorphous and **crystalline** forms of **losartan potassium**)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD

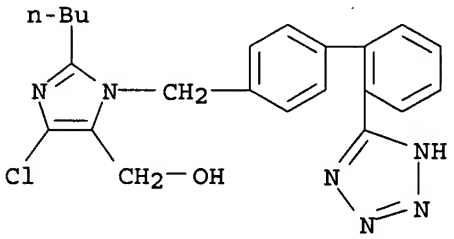
RE

(1) Chiu; US 5140037 A 1992 HCAPLUS

IT **124750-99-8, Losartan potassium**
539820-64-9 539820-65-0 539820-66-1
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(amorphous and **crystalline** forms of **losartan potassium**)

RN 124750-99-8 HCAPLUS

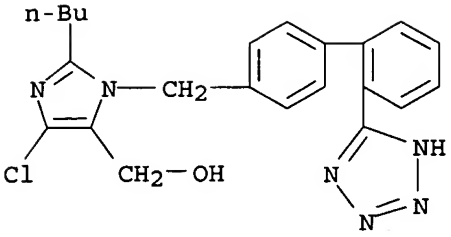
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



● K

RN 539820-64-9 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt, monohydrate (9CI) (CA INDEX NAME)



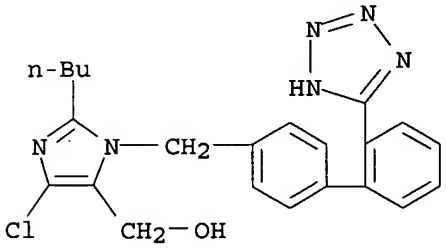
● K

● H_2O

RN 539820-65-0 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, compd. with ethanol (1:1), monopotassium salt (9CI) (CA INDEX NAME)

CM 1

CRN 114798-26-4
CMF C22 H23 Cl N6 O

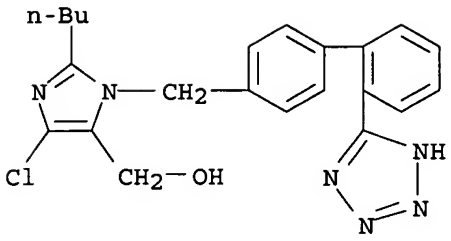


CM 2

CRN 64-17-5
CMF C2 H6 O

H_3C-CH_2-OH

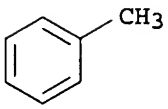
RN 539820-66-1 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt, tetrahydrate (9CI) (CA INDEX NAME)



● K

● 4 H_2O

IT **108-88-3**, **Toluene**, processes **110-54-3**, **Hexane**, processes **141-78-6**, **Ethyl acetate**, processes
RL: **PEP (Physical, engineering or chemical process)**; **PYP (Physical process)**; **PROC (Process)**
(amorphous and **crystalline** forms of **losartan potassium**)
RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



RN 110-54-3 HCAPLUS
CN Hexane (8CI, 9CI) (CA INDEX NAME)

Me— $(CH_2)_4$ —Me

RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

L48 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:906207 HCAPLUS
DN 138:4604
ED Entered STN: 29 Nov 2002
TI Deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I
IN Ramashankar; Reddy, Ravinder Vennapu; Sivakumaran, Meenakshisunderam;

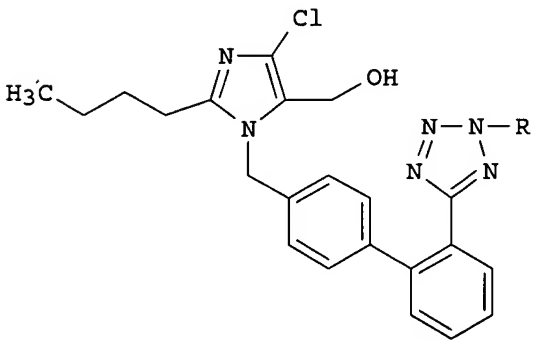
Handa, Vijay Kumar
PA Aurobindo Pharma Limited, India
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-10
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 45, 63, 75
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002094816	A1	20021128	WO 2001-IN205	20011120 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1294712	A1	20030326	EP 2001-274254	20011120 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
SI 21236	C	20031231	SI 2001-20042	20011120 <--
JP 2004520446	T2	20040708	JP 2002-591489	20011120 <--
BG 107478	A	20040130	BG 2003-107478	20030117 <--
PRAI IN 2001-MA403	A	20010518 <--		
IN 2001-CH403	A	20010518 <--		
WO 2001-IN205	W	20011120 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002094816	ICM	C07D403-10
WO 2002094816	ECLA	C07D403/10+257+233 <--
JP 2004520446	FTERM	4C063/AA01; 4C063/BB06; 4C063/CC47; 4C063/DD25; 4C063/EE01; 4C063/EE10 <--

OS CASREACT 138:4604; MARPAT 138:4604
GI



I

AB The polymorphic **crystalline** form I of **losartan**

potassium (I; R = K) is prepared in high yield and selectivity by the deprotection of a **losartan** precursor (I; R = H, CPh3; e.g., trityl lorsartan) with potassium hydroxide in an alc. (e.g., methanol), followed by reducing the alc. concentration under vacuum, and adding a nonsolvent (e.g., acetone) to precipitate the **losartan potassium.**

ST **losartan potassium crystal** polymorphism; nonsolvent pptn potassium **crystal** polymorphism

IT Neutralization
Polymorphism (**crystal**)
(deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I)

IT Precipitation (chemical)
(in a deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I using a nonsolvent)

IT Alcohols, uses
RL: NUU (Other use, unclassified); **REM (Removal or disposal)**; **PROC (Process)**; USES (Uses)
(solvents; deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I)

IT **124750-99-8P, Losartan potassium**
RL: **IMF (Industrial manufacture)**; **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP (Physical process)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **PROC (Process)**
(deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I)

IT **114798-26-4, Losartan** 133909-99-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I)

IT 1310-58-3, Potassium hydroxide, reactions
RL: RCT (Reactant); RGT (Reagent); RACT (Reactant or reagent)
(in a deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I)

IT 67-64-1, Acetone, uses 75-05-8, Acetonitrile, uses **108-88-3, Toluene**, uses **141-78-6, Ethyl acetate**
, uses
RL: NUU (Other use, unclassified); USES (Uses)
(nonsolvent; in a deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I)

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 71-23-8, Propanol, uses 71-36-3, Butanol, uses
RL: NUU (Other use, unclassified); **REM (Removal or disposal)**; **PROC (Process)**; USES (Uses)
(solvent; in a deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

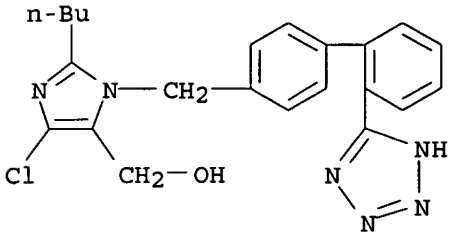
RE

(1) Carini, D; US 5138069 A 1992 HCAPLUS
(2) Du Pont; WO 9310106 A 1993 HCAPLUS
(3) Kennedy, M; WO 9818787 A 1998 HCAPLUS

IT **124750-99-8P, Losartan potassium**
RL: **IMF (Industrial manufacture)**; **PEP (Physical, engineering or chemical process)**; PRP (Properties); **PYP**

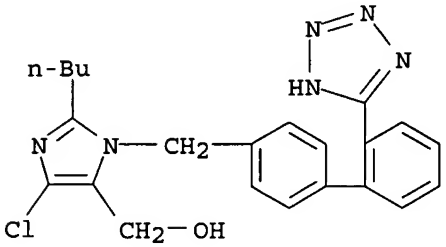
(Physical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
(deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I)

RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



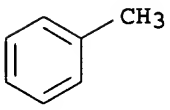
IT **114798-26-4, Losartan**
RL: RCT (Reactant); RACT (Reactant or reagent)
(deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **crystalline** form I)

RN 114798-26-4 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

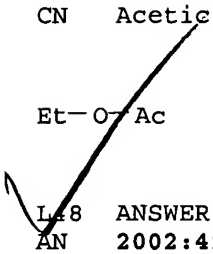


IT **108-88-3, Toluene**, uses **141-78-6, Ethyl acetate**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(nonsolvent; in a deprotection process for the **crystallization** of **losartan potassium** in the polymorphic **cryst**
. form I)

RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



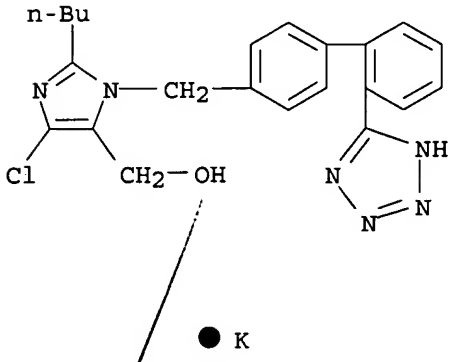
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)



L48 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:496878** HCAPLUS
DN **137:286738**
ED Entered STN: 02 Jul 2002
TI **Losartan potassium**, a non-peptide agent for the treatment of arterial hypertension
AU Fernandez, Daniel; Vega, Daniel; Ellena, Javier A.; Echeverria, Gustavo
CS Escuela de Ciencia y Tecnologia, Universidad Nacional de General San Martin, Buenos Aires, Argent.
SO Acta Crystallographica, Section C: Crystal Structure Communications (**2002**), C58(7), m418-m420
CODEN: ACSCEE; ISSN: 0108-2701
PB Blackwell Munksgaard
DT Journal
LA English
CC 75-8 (Crystallography and Liquid Crystals)
Section cross-reference(s): 28
AB **Crystals** of the title compound, potassium 2-butyl-4-chloro-1-{[2'-(5-tetrazolido)biphenyl-4-yl]methyl}-1H-imidazol-5-ylmethanol, are monoclinic, space group P21/c, with a 15.5724(3), b 7.4976(2), c 24.2640(5) Å,, β 128.4980(10)°; Z = 4, dc = 1.381; R = 0.043, Rw(F2) = 0.116 for 3888 reflections. The imidazole and tetrazole rings are at angles of 85.0(2) and 51.8(1)°, resp., to the Ph rings to which they are attached, while the dihedral angle between the latter two rings is 46.7(1)°. The coordination sphere of the metal cation consists of six tetrazolyl N atoms, the MeOH O atom and the π cloud of one of the Ph rings. These interactions determine the formation of columns of mol. anions that lie parallel to the b axis, while H bonding contributes to intercolumnar cohesion. Far from the center of the columns, the hydrocarbon chain is immersed in a hydrophobic environment.
ST **crystal** structure **losartan potassium**; mol structure **losartan potassium**; hydrogen bond **losartan potassium**; potassium butylchlorotetrazolylbiphenylylmethylimidazolemethanol **crystal** structure
IT **Crystal** structure
Hydrogen bond
Molecular structure
(of **losartan potassium**)
IT **124750-99-8, Losartan potassium**
RL: PRP (Properties)
(**crystal** structure of)
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Allen, F; Acc Chem Res 1983, V16, P146 HCAPLUS
(2) Birkenhager, W; J Hypertens 1999, V17, P873 HCAPLUS
(3) Blessing, R; Acta Cryst 1995, VA51, P33 HCAPLUS
(4) Farrugia, L; J Appl Cryst 1999, V32, P837
(5) Gavras, H; Clin Ther 1996, V18, P1058 MEDLINE
(6) Goa, K; Drugs 1996, V51, P820 HCAPLUS
(7) Johnson, A; Drug News Perspect 1990, V3, P337
(8) Nardelli, M; J Appl Cryst 1995, V28, P659 HCAPLUS

(9) Nonius BV; COLLECT 1997-2000
(10) Okazaki, T; Chem Pharm Bull 1998, V46, P69 HCAPLUS
(11) Otwinowski, Z; Methods in Enzymology, Macromolecular Crystallography, Part A 1997, V276, P307 HCAPLUS
(12) Raghavan, K; Pharm Res 1993, V10, P900 HCAPLUS
(13) Sheldrick, G; SHELXS97 and SHELXL97 1997
(14) Sheldrick, G; SHELXTL/PC. Release 4.2 1991
(15) Vega, D; Acta Cryst 2001, VC57, P1092 HCAPLUS
(16) Wexler, R; J Med Chem 1996, V39, P625 HCAPLUS
(17) Wu, L; Pharm Res 1993, V10, P1793 HCAPLUS

IT **124750-99-8, Losartan potassium**
RL: PRP (Properties)
(**crystal** structure of)
RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



L48 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:798216** HCAPLUS
DN **135:344489**
ED Entered STN: 02 Nov 2001
TI Detritylation process for the synthesis of **losartan potassium** using potassium hydroxide and a C1-4 alkanol solvent
IN Fischer, Janos; Ballo, Ildiko; Petenyi, Endrene; Kreidl, Janos; Czibula, Laszlo; Nemes, Andras; Deutsch Juhasz, Ida; Werk Papp, Eva; Nagy Bagdy, Judit; Hegedus, Istvan; Farkas, Jenome
PA Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SO PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-10
ICS A61K031-41; A61P009-12; C07D403-10; C07D257-00; C07D233-99
CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 45, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001081336	A1	20011101	WO 2001-HU47	20010420 <--
	WO 2001081336	C1	20020829		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,

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            LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
            RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
            VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    AU 2001054998        A5    20011107    AU 2001-54998          20010420 <--
    EP 1274702           A1    20030115    EP 2001-928134         20010420 <--
    EP 1274702           B1    20040211
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
    JP 2003531203        T2    20031021    JP 2001-578426         20010420 <--
    EE 200200460         A     20031215    EE 2002-460            20010420 <--
    AT 259366            E     20040215    AT 2001-928134         20010420 <--
    ES 2215130           T3    20041001    ES 2001-1928134        20010420 <--
    US 2003078435        A1    20030424    US 2002-182109         20020724 <--
    US 6710183           B2    20040323
    BG 107031            A     20030829    BG 2002-107031         20020823 <--
PRAI HU 2000-1618        A     20000421  <--
    WO 2001-HU47         W     20010420  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 2001081336    ICM    C07D403-10
                  ICS    A61K031-41; A61P009-12; C07D403-10; C07D257-00;
                         C07D233-99
 WO 2001081336    ECLA   C07D403/10+257+233                              <--
 US 2003078435    NCL    548/253.000
                  ECLA   C07D403/10+257+233                              <--
OS   CASREACT 135:344489; MARPAT 135:344489
AB   Losartan potassium (m.p. 262-264°) is prepared in
     high yield and selectivity by reacting the corresponding tritylated derivative
     [e.g., 2-butyl-4-chloro-1-[[2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-1,1'-
     biphenyl-4-yl]methyl]-1H-imidazole-4-methanol] in an C1-4 alkanol (e.g.,
     methanol) solvent with 0.1-1 equiv of potassium hydroxide and isolating
     the product after crystallizing out by changing the solvent to an
     aprotic (e.g., acetonitrile) or weakly protic solvent.
ST   losartan potassium prepn detritylation process
IT   Alcohols, uses
     RL: NUU (Other use, unclassified); USES (Uses)
        (aliphatic, C1-4, solvents; detritylation process for the synthesis of
        losartan potassium using potassium hydroxide and a
        C1-4 alkanol solvent)
IT   Crystallization
        (detritylation process for the synthesis of losartan
        potassium using potassium hydroxide and a C1-4 alkanol solvent
        followed by)
IT   Methylation
        (tritylation, retro; detritylation process for the synthesis of
        losartan potassium using potassium hydroxide and a
        C1-4 alkanol solvent)
IT   75-05-8, Acetonitrile, uses   78-92-2, sec-Butanol
     RL: NUU (Other use, unclassified); USES (Uses)
        (crystallization solvent; detritylation process for the synthesis of
        losartan potassium using potassium hydroxide and a
        C1-4 alkanol solvent)
IT   1310-58-3, Potassium hydroxide, reactions   133909-99-6
     RL: RCT (Reactant); RACT (Reactant or reagent)
        (detritylation process for the synthesis of losartan
        potassium using potassium hydroxide and a C1-4 alkanol solvent)
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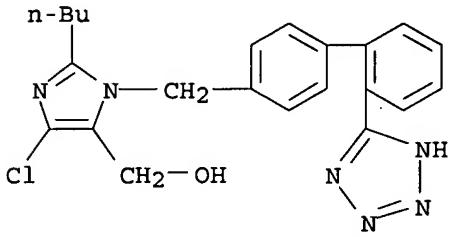
IT **124750-99-8P, Losartan potassium**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(detritylation process for the synthesis of **losartan potassium** using potassium hydroxide and a C1-4 alkanol solvent)
IT 67-56-1, Methanol, uses 108-10-1, MIBK
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; detritylation process for the synthesis of **losartan potassium** using potassium hydroxide and a C1-4 alkanol solvent)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Du Pont; EP 0324377 A 1989 HCAPLUS
(2) Du Pont; WO 9310106 A 1993 HCAPLUS
(3) Merck & Co Inc; WO 9517396 A 1995 HCAPLUS
IT **124750-99-8P, Losartan potassium**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(detritylation process for the synthesis of **losartan potassium** using potassium hydroxide and a C1-4 alkanol solvent)
RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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L48 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:45216 HCAPLUS
DN 130:115010
ED Entered STN: 22 Jan 1999
TI Process for the **crystallization** of **losartan**
IN Breen, Patrick; Dienemann, Erik A.; Epstein, Albert D.; Larson, Karen A.; Kennedy, Michael T.; Mahadevan, Hari
PA Merck and Co., Inc., USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D257-04
ICS A61K031-14
INCL 548252000
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5859258	A	19990112	US 1997-959209	19971028 <--
PRAI US 1997-959209		19971028 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 5859258	ICM	C07D257-04
	ICS	A61K031-14
	INCL	548252000
US 5859258	NCL	548/252.000
	ECLA	C07D403/10+257+233 <--

AB **Losartan potassium** (I) is an angiotensin II antagonist useful in the treatment of hypertension and congestive heart failure. This invention relates to the process for the controlled **crystallization** of **losartan potassium** utilizing anti-solvent addition combined with massive seeding in order to obtain the desired **crystal** morphol. and bulk phys. properties necessary for successful formulation. Isopropanol 25.4 kg and 8.0 kg I were charged to a vessel along with 930 mL of distilled water. In a sep. vessel, 12.4 kg **cyclohexane** and 40 g I milled seed were heated to 60-65° and added to the above vessel until the solution became cloudy. The KF (Karl Fischer titration) at which the cloud point occurred was 1.90 % and the amount of **cyclohexane** slurry used to reach the cloud point was 6.2 kg. The batch was then seeded with 400 g finely-milled I and aged at reflux (70°) for 1 h. The batch was distilled at constant volume with simultaneous addition of 35 kg of 75:25 **cyclohexane**:isopropanol to achieve a batch KF of 0.54%. Distillates were collected with addition of 6 kg of **cyclohexane** to the batch during the concentration step. The batch was filtered under a N atmospheric and the cake was washed with 20 kg of 75:25 **cyclohexane**:isopropanol followed by 20 kg of **cyclohexane**. The batch was dried on trays at 45-50° under vacuum to obtain highly purified **crystals** of I.

ST **losartan potassium crystn**

IT Antihypertensives
Crystal nucleation
Crystallization
Milling (size reduction)
(**crystallization** of **losartan potassium**)

IT Heart, disease
(failure; **crystalline losartan potassium** for treatment of)

IT 11128-99-7, Angiotensin II
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonist; **crystallization** of **losartan potassium**)

IT **110-82-7, Cyclohexane**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(as antisolvent; **crystallization** of **losartan potassium**)

IT **124750-99-8, Losartan potassium**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization** of **losartan potassium**)

IT 67-63-0, Isopropanol, uses
RL: NUU (Other use, unclassified); USES (Uses)
(distillation in; **crystallization** of **losartan potassium**)

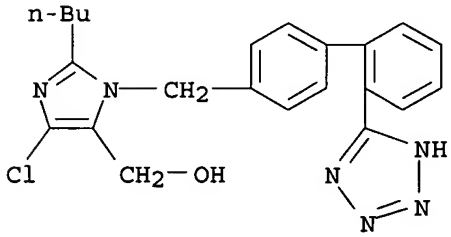
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; WO 9310106 A1 1993 HCAPLUS
(2) Anon; WO 9517396 1995 HCAPLUS
(3) Campbell; US 5608075 1997 HCAPLUS
(4) Carini; US 5138069 1992 HCAPLUS

(5) Lo; US 5130439 1992 HCAPLUS
(6) Lo; US 5206374 1993 HCAPLUS
(7) Lo; US 5310928 1994 HCAPLUS
IT **110-82-7**, **Cyclohexane**, uses
RL: NUU (Other use, unclassified); USES (Uses)
(as antisolvent; **crystallization of losartan potassium**)
RN 110-82-7 HCAPLUS
CN Cyclohexane (8CI, 9CI) (CA INDEX NAME)

IT **124750-99-8**, **Losartan potassium**
RL: **PEP (Physical, engineering or chemical process)**; PRP (Properties); THU (Therapeutic use); BIOL (Biological study); **PROC (Process)**; USES (Uses)
(**crystallization of losartan potassium**)
RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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L48 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:293497 HCAPLUS
DN 128:326548
ED Entered STN: 20 May 1998
TI Process for the **crystallization** of **losartan**
IN Breen, Patrick; Dienemann, Erik A.; Epstein, Albert D.; Larson, Karen A.; Kennedy, Michael T.; Mahadevan, Hari
PA Merck & Co., Inc., USA; Breen, Patrick; Dienemann, Erik A.; Epstein, Albert D.; Larson, Karen A.; Kennedy, Michael T.; Mahadevan, Hari
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D403-10
CC 63-6 (Pharmaceuticals)
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

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            MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US,
            UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
            GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
            GN, ML, MR, NE, SN, TD, TG
     AU 9850898            A1    19980522    AU 1998-50898           19971024 <--
     EP 937068             A1    19990825    EP 1997-913800          19971024 <--
     EP 937068             B1    20020313
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
            FI, RO
     BR 9712390            A     19990831    BR 1997-12390           19971024 <--
     CN 1241186            A     20000112    CN 1997-180909          19971024 <--
     CN 1101393            B     20030212
     JP 2000504343         T2    20000411    JP 1998-520675          19971024 <--
     JP 3249827            B2    20020121
     AT 214388             E     20020315    AT 1997-913800          19971024 <--
     PT 937068             T     20020731    PT 1997-913800          19971024 <--
     ES 2173433            T3    20021016    ES 1997-913800          19971024 <--
     SK 282875             B6    20030109    SK 1999-570             19971024 <--
     HR 970565             B1    20030228    HR 1997-970565          19971024 <--
     CZ 291672             B6    20030416    CZ 1999-1515            19971024 <--
     TW 411338             B     20001111    TW 1997-86116083        19971029 <--
PRAI US 1996-29326P        P     19961029  <--
     GB 1996-25804         A     19961212  <--
     US 1996-29326         P     19961029  <--
     WO 1997-US19442       W     19971024  <--
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
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 WO 9818787       ECLA   C07D403/10+257+233                              <--
 CN 1241186       ECLA   C07D403/10+257+233                              <--
AB   Losartan potassium is an angiotensin II antagonist
     useful in the treatment of hypertension and congestive heart failure.
     This invention relates to the process for the controlled crystallization
     of losartan potassium utilizing anti-solvent addition
     combined with massive seeding in order to obtain the desired
     crystal morphol. and bulk phys. properties necessary for
     successful formulation.
ST   losartan crystn
IT   Cloud point
       Crystallization
     Particle size
        (crystallization of losartan)
IT   67-63-0, Isopropanol, processes 110-82-7, Cyclohexane,
     processes
     RL: PEP (Physical, engineering or chemical process); PROC (Process)
        (crystallization of losartan)
IT   114798-26-4, Losartan 124750-99-8,
     Losartan potassium
     RL: PEP (Physical, engineering or chemical process); PRP
     (Properties); THU (Therapeutic use); BIOL (Biological study); PROC
     (Process); USES (Uses)
        (crystallization of losartan)
RE.CNT  2     THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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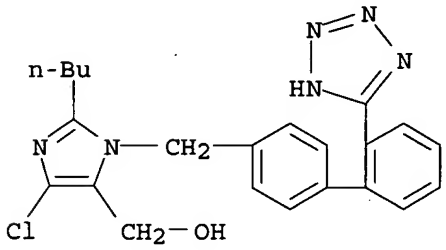
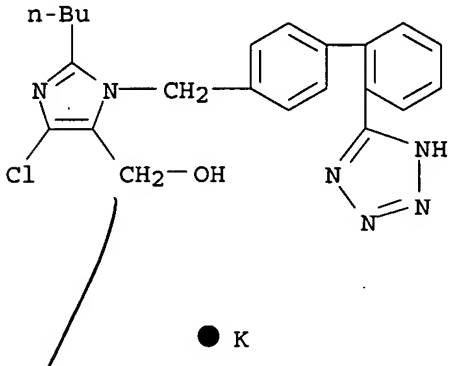
(1) Campbell; WO 9517396 A 1995 HCAPLUS
(2) Du Pont; WO 9310106 A 1993 HCAPLUS
IT **110-82-7**, **Cyclohexane**, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(**crystallization** of **losartan**)
RN 110-82-7 HCAPLUS
CN Cyclohexane (8CI, 9CI) (CA INDEX NAME)

IT **114798-26-4**, **Losartan 124750-99-8**,
Losartan potassium
RL: **PEP (Physical, engineering or chemical process)**; PRP
(Properties); THU (Therapeutic use); BIOL (Biological study); **PROC**
(Process); USES (Uses)
(**crystallization** of **losartan**)
RN 114798-26-4 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



L48 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:671389 HCAPLUS

DN 119:271389
ED Entered STN: 25 Dec 1993
TI Tetrazolylphenylboronic acid intermediates for the synthesis of angiotensin II receptor antagonists
IN Lo, Young Sek; Rossano, Lucius Thomas; Larsen, Robert D.; King, Anthony O.
PA du Pont de Nemours, E. I., and Co., USA; Merck and Co., Inc.
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D257-02
CC 29-4 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 1, 28
FAN.CNT 3

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PI	WO 9310106	A1	19930527	WO 1992-US9979	19921118	<--
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	US 5130439	A	19920714	US 1991-793514	19911118	<--
	US 5206374	A	19930427	US 1992-911813	19920710	<--
	US 5310928	A	19940510	US 1992-911812	19920710	<--
	AU 9331792	A1	19930615	AU 1993-31792	19921118	<--
	AU 665388	B2	19960104			
	EP 643704	A1	19950322	EP 1993-900550	19921118	<--
	EP 643704	B1	20030917			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE					
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	PL 171453	B1	19970430	PL 1992-303787	19921118	<--
	PL 176124	B1	19990430	PL 1992-312131	19921118	<--
	SK 280887	B6	20000912	SK 1994-579	19921118	<--
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	FI 9402282	A	19940517	FI 1994-2282	19940517	<--
	FI 112945	B1	20040213			
	NO 9401857	A	19940718	NO 1994-1857	19940518	<--
	NO 307932	B1	20000619			
PRAI	US 1991-793514	A	19911118	<--		
	US 1992-911812	A	19920710	<--		
	US 1992-911813	A	19920710	<--		
	WO 1992-US9979	A	19921118	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9310106	ICM	C07D257-02	
US 5130439	NCL	548/110.000	<--
US 5206374	NCL	548/110.000	<--
US 5310928	NCL	548/252.000; 548/250.000; 548/254.000	
	ECLA	C07F005/02C; C07F005/05	<--

OS CASREACT 119:271389; MARPAT 119:271389
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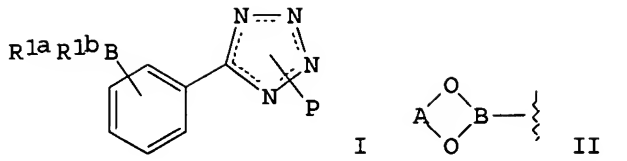

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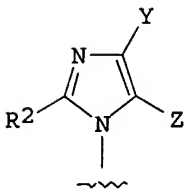

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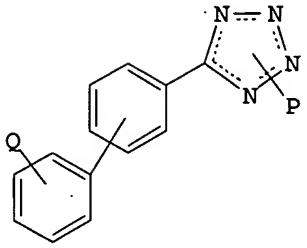


V

AB Title compds. I [P = Ph3C, Me3C, C1-4-alkoxymethyl, MeSCH2, Ph-C1-4-alkoxymethyl, p-MeOC6H4CH2, 2,4,6-trimethylbenzyl, 2-(trimethylsilyl)ethyl, tetrahydropyranyl, piperonyl, benzenesulfonyl; R1a, R1b = independently Cl, Br, C1-4-alkoxy, OH; or R1aBR1b = II, A = Ph (sic) or (CH2)n, n = 2-4] were prepared as intermediates for the synthesis of angiotensin II receptor antagonists. Thus, reaction of B(OCHMe2)3 with the Li salt of 5-phenyl-2-trityltetrazole carbanion (generated from 5-phenyl-2-trityltetrazole and BuLi), followed by AcOH/H2O hydrolysis, afforded title compound I (P = 2'-Ph3C, R1a = R1b= OH) (III). More advanced intermediates that are precursors for angiotensin II receptor antagonists are prepared by cross-coupling of I with QC6H4X [X = Br, I, methanesulfonyloxy, toluenesulfonyloxy, fluorosulfonyloxy, trifluoromethanesulfonyloxy; Q = H, Me, C1-4-alkyl, hydroxymethyl, triorganosiloxymethyl, hydroxy-C1-4-alkyl, formyl, C1-4-acyl, C1-4-alkoxycarbonyl, WL [L = single bond, (CH2)t, t = 1-4, (CH2)rO(CH2)r, (CH2)rSOr(CH2)r, r = 0-2] and W = IV (R2 = C1-4-alkyl, Y = e.g., C1-4-alkyl, Z = e.g., hydroxymethyl)] in presence of metal catalyst, base, and coupling solvent to afford biphenyls V. Coupling of III with QC6H4X [X = 4-Br; Q = WL [L = CH2, W = IV (R2 = Bu, Y = Cl, Z = CH2OH)]] with catalyst formed from Pd chloride, Ph3P, and P(OCHMe2)3 afforded the corresponding V in 90% yield.

ST tetrazolylphenylboronic acid angiotensin II receptor antagonist; boronic acid tetrazolylphenyl intermediate receptor antagonist; boration phenyltetrazole; cross coupling **benzene** deriv tetrazolylphenylboronic acid; biphenyl tetrazolyl angiotensin II receptor antagonist

IT Receptors
RL: SPN (Synthetic preparation); PREP (Preparation)
(angiotensin II, tetrazolophenylboronic acid intermediates for synthesis of, preparation of)

IT Substitution reaction
(boration, of phenyltetrazole in preparation of angiotensin II receptor antagonist intermediates)

IT Coupling reaction
(cross-, of tetrazolophenylboronic acids with electrophiles in preparation of angiotensin II receptor antagonist intermediates, catalytic)

IT Coupling reaction catalysts
(cross-, palladium complexes, with or without phase-transfer catalysts, for preparation of angiotensin II receptor antagonist intermediates)

IT 589-15-1, p-Bromobenzyl bromide 139964-22-0

RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation reaction of, in preparation of angiotensin II receptor antagonist intermediates)

IT 150097-92-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation reaction of, in preparation of, as angiotensin II receptor antagonist intermediate)

IT 121-44-8, Triethylamine, uses 122-08-7 497-19-8, Carbonic acid disodium salt, uses 534-17-8, Cesium carbonate 584-08-7, Potassium carbonate 2052-49-5, Tetrabutylammonium hydroxide 7087-68-5, Diisopropylethylamine 12026-06-1, Thallium hydroxide 26628-22-8, Sodium azide (Na(N3))
RL: RCT (Reactant); RACT (Reactant or reagent)
(base, for preparation of angiotensin II receptor antagonist intermediates)

IT 17351-62-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(base, in cross-coupling reaction for preparation of angiotensin II receptor antagonist intermediates)

IT 18039-42-4, 5-Phenyltetrazole
RL: RCT (Reactant); RACT (Reactant or reagent)
(boration reaction of, in preparation of angiotensin II receptor antagonist intermediates)

IT 5419-55-6, Triisopropyl borate
RL: RCT (Reactant); RACT (Reactant or reagent)
(boration reaction with, in preparation of angiotensin II receptor antagonist intermediates)

IT 14221-01-3, Tetrakis(triphenylphosphine)palladium
RL: CAT (Catalyst use); USES (Uses)
(catalysts, for cross-coupling reactions in preparation of angiotensin II receptor antagonist intermediates)

IT 873-75-6, p-Bromobenzyl alcohol
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling reaction of, in preparation of angiotensin II receptor antagonist intermediate)

IT 1122-91-4, p-Bromobenzaldehyde 151012-32-7 151012-33-8 151012-34-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling reaction of, in preparation of angiotensin II receptor antagonist intermediates)

IT 116-17-6, Triisopropylphosphite 603-35-0, Triphenylphosphine, uses 7647-10-1, Palladium chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling-reaction catalysts formed in situ from, for preparation of angiotensin II receptor antagonist intermediates)

IT 557-20-0, Diethylzinc
RL: RCT (Reactant); RACT (Reactant or reagent)
(cross-coupling reaction catalysts activated with, for preparation of angiotensin II receptor antagonist intermediates)

IT 3375-31-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(cross-coupling reaction catalysts from, for preparation of angiotensin II receptor antagonist intermediates)

IT 13965-03-2 14588-08-0 15630-11-2 19978-61-1 23523-33-3 29964-62-3 32005-36-0 51364-51-3, Tris(dibenzylideneacetone)dipalladium 59831-02-6 60767-63-7 70191-37-6 73727-99-8 86381-25-1 149796-59-8 151037-11-5 151037-12-6 151037-13-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(cross-coupling reaction catalysts, for preparation of angiotensin II receptor antagonist intermediates)

IT 106-38-7, p-Bromotoluene
RL: RCT (Reactant); RACT (Reactant or reagent)

(cross-coupling reaction of, in preparation of angiotensin II receptor antagonist intermediate)

IT 87268-78-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(formation and boration of, in preparation of angiotensin II receptor antagonist intermediates)

IT 143722-26-3P 143722-27-4P 151012-28-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(formation and boration reaction of, in preparation of angiotensin II receptor antagonist intermediates)

IT **151012-29-2P**
RL: RCT (Reactant); **SPN (Synthetic preparation)**; **PREP (Preparation)**; RACT (Reactant or reagent)
(formation and neutralization of, in preparation of angiotensin II receptor antagonist intermediates)

IT 133910-00-6P 138804-35-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(formation and reduction of, in preparation of angiotensin II receptor antagonist intermediates)

IT 623-00-7, p-Bromobenzonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(heterocyclization and boration reactions of, in preparation of angiotensin II receptor antagonist intermediate)

IT 6952-59-6, m-Bromobenzonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(heterocyclization reaction of, with sodium azide in preparation of angiotensin II receptor antagonist intermediates)

IT 1643-19-2, Tetrabutylammonium bromide
RL: RCT (Reactant); RACT (Reactant or reagent)
(phase-transfer cross-coupling catalysts, for preparation of angiotensin II receptor antagonist intermediates)

IT 133909-97-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and bromination of, in preparation of angiotensin II receptor antagonist intermediates)

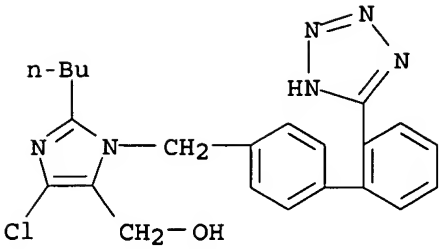
IT 143722-25-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling reaction of, in preparation angiotensin II receptor antagonist intermediates)

IT 143722-29-6P 151012-31-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling reaction of, in preparation of angiotensin II receptor antagonist intermediates)

IT 133909-99-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of, in preparation of angiotensin II receptor antagonist intermediates)

IT 133051-88-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of angiotensin II receptor antagonist intermediates)

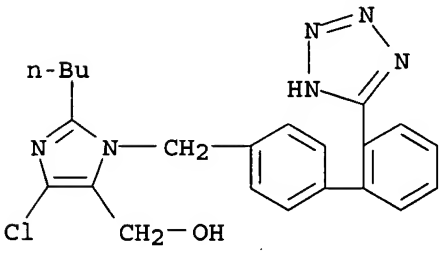
IT 135050-95-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and sulfonylation of, in preparation of angiotensin II receptor antagonist intermediates)
IT **114798-26-4P 124750-99-8P** 143722-30-9P 143722-31-0P
150097-93-1P 151012-30-5P
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, as angiotensin II receptor antagonist intermediate)
IT 73680-73-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as base for preparation of angiotensin II receptor antagonist
intermediates)
IT 76-83-5, Triphenylchloromethane 83857-96-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of angiotensin II receptor antagonist intermediates)
IT 100-85-6, Benzyltrimethylammonium hydroxide
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ammonium carbonate in preparation of angiotensin II receptor antagonist intermediates)
IT 506-87-6, Ammonium carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with benzyltrimethylammonium hydroxide in preparation of angiotensin II receptor antagonist intermediates)
IT 108-10-1, Methyl isobutyl ketone
RL: RCT (Reactant); RACT (Reactant or reagent)
(**recrystn.** solvent, for preparation of angiotensin II receptor antagonist intermediates)
IT **60-29-7**, **Diethyl ether**, uses 64-17-5,
Ethanol, uses 67-56-1, Methanol, uses 67-68-5, uses 68-12-2, DMF,
uses 71-23-8, Propanol, uses **71-43-2**, **Benzene**, uses
75-05-8, Acetonitrile, uses 96-47-9, 2-Methyltetrahydrofuran
108-88-3, **Toluene**, uses 109-99-9, uses 123-91-1,
1,4-Dioxane, uses 127-19-5, Dimethylacetamide 462-95-3,
Diethoxymethane 7732-18-5, Water, uses
RL: RCT (Reactant); RACT (Reactant or reagent)
(solvent, for preparation of angiotensin II receptor antagonist intermediates)
IT 124-63-0, Methanesulfonyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(sulfonylation with, in preparation of angiotensin II receptor antagonist intermediates)
IT 998-40-3, Tributylphosphine
RL: RCT (Reactant); RACT (Reactant or reagent)
(use of, for purification of angiotensin II receptor antagonist intermediates)
IT **151012-29-2P**
RL: RCT (Reactant); **SPN (Synthetic preparation); PREP (Preparation)**; RACT (Reactant or reagent)
(formation and neutralization of, in preparation of angiotensin II receptor antagonist intermediates)
RN 151012-29-2 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt, hydrochloride (9CI) (CA INDEX NAME)



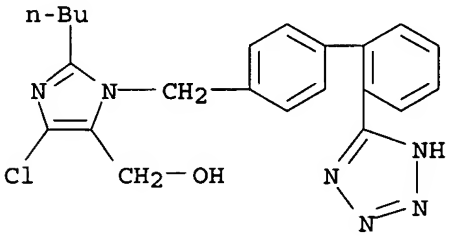
● x HCl

● K

IT **114798-26-4P 124750-99-8P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of, as angiotensin II receptor antagonist intermediate)
RN 114798-26-4 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

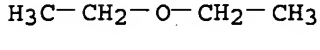


RN 124750-99-8 HCAPLUS
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



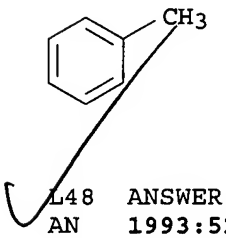
● K

IT **60-29-7**, **Diethyl ether**, uses **71-43-2**
, **Benzene**, uses **108-88-3**, **Toluene**, uses
RL: RCT (Reactant); RACT (Reactant or reagent)
(solvent, for preparation of angiotensin II receptor antagonist intermediates)
RN 60-29-7 HCAPLUS
CN Ethane, 1,1'-oxybis- (9CI) (CA INDEX NAME)

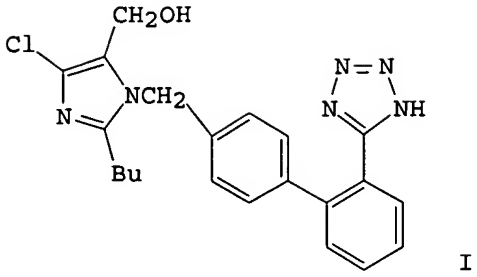


RN 71-43-2 HCAPLUS
CN Benzene (8CI, 9CI) (CA INDEX NAME)

RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



L48 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1993:525045** HCAPLUS
DN **119:125045**
ED Entered STN: 18 Sep 1993
TI A spectroscopic investigation of **Losartan** polymorphs
AU Raghavan, Krishnaswamy; Dwivedi, Anil; Campbell, G. Creston, Jr.; Johnston, Eric; Levorse, Dorothy; McCauley, James; Hussain, Munir
CS Exp. Stn., Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0400, USA
SO Pharmaceutical Research (**1993**), 10(6), 900-4
CODEN: PHREEB; ISSN: 0724-8741
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
GI



I

AB **Losartan** (I), an antihypertensive agent in clin. development, existed in 2 enantiotropic polymorphic forms, a low-temperature stable form (Form I) and a high-temperature stable form (Form II), the temps. at which they are stable being related to the transition temperature X-ray **powder** diffraction patterns indicated differences in the **crystal** packing of the 2 forms. The vibrational data from IR and Raman spectroscopy suggested a subtle change in mol. conformation and **crystal** packing in the 2 forms. Solid-state 13C NMR data of the polymorphs concurred with the vibrational data and indicated that, while the observed line widths reflect no major changes in **crystallinity**, signal multiplicities and chemical shifts do reflect differences in mol. packing in the resp. unit cells. Thus, in the absence of **crystallog.** data, useful structural information could be derived from spectroscopic results to identify each of the **crystalline** forms.

ST spectroscopy **losartan** polymorph

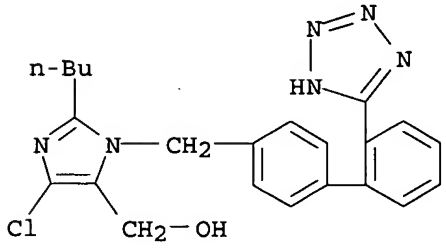
IT **Crystal morphology**
Infrared spectra
Nuclear magnetic resonance
Raman spectra
(of **Losartan** polymorphs)

IT **114798-26-4, Losartan 124750-99-8**
RL: BIOL (Biological study)
(polymorphs, spectroscopy study of)

IT **114798-26-4, Losartan 124750-99-8**
RL: BIOL (Biological study)
(polymorphs, spectroscopy study of)

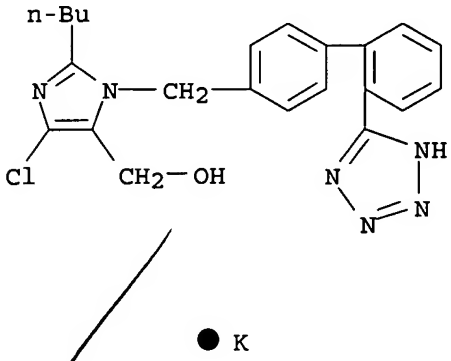
RN 114798-26-4 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)

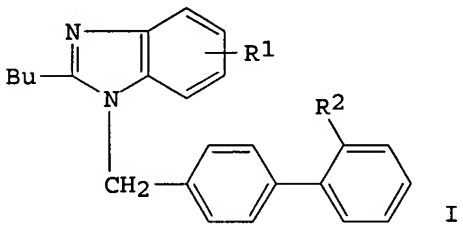


RN 124750-99-8 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



L48 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:408736 HCAPLUS
DN 119:8736
ED Entered STN: 10 Jul 1993
TI Nonpeptide angiotensin II receptor antagonist. Synthesis and biological activity of benzimidazoles
AU Kubo, Keiji; Inada, Yoshiyuki; Kohara, Yasuhisa; Sugiura, Yoshihiro; Ojima, Mami; Itoh, Katsuhiko; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko
CS Pharm. Group, Takeda Chem. Ind., Ltd., Yodogawaku, 532, Japan
SO Journal of Medicinal Chemistry (**1993**), 36(12), 1772-84
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 75
GI



I

AB A series of substituted 2-butylbenzimidazoles I (R1 = H, 5-, 6-, 7-OMe,5-, 6-Cl, 4-, 5- 6-, 7-CO2Me, 5-Me-7-CO2Me, 5-Cl-7-CO2Me, 6-Me-7-CO2Et, 4-CO2NH2, 7-CO2Et, 7-CO2Bu, 4-, 5-, 6-, 7-CO2H, 5-Me-7-CO2H, 5-Cl-7-CO2H, 6-Me-7-CO2H, 7-CONHCHMe2, 7-CH2OH, 7-CH2OMe, 7-CH2NMe2, 7-Me, 7-CH2CO2Et, 7-OH, 7-CH2CO2H, R2 = 5-tetrazolyl; R1 = H, 7-CO2H, R2 = CO2H; R1 = 7-CO2H, R2 = 1-methyl-5-tetrazolyl) bearing a biphenylylmethyl moiety at the 1-position was prepared via three synthetic routes and evaluated for angiotensin II (AII) receptor antagonistic activity (in vitro and in vivo). Binding affinity was determined using bovine adrenal cortical membrane. Substitution at the 4-, 5-, or 6-position reduced the affinity relative to that of the unsubstituted compound I (R1 = H, R2 = 5-tetrazolyl). However, most of the compds. with a substituent at the 7-position showed binding affinity comparable to that of **DuP753** (**losartan**). In

functional studies, a carboxyl group was found to be very important for antagonistic activity against AII. Comparison of 2-butyl-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-4-, 5-, 6-, and -7-carboxylic acids (I; R1 = 4-, 5-, 6-, 7-CO2H, R2 = 5-tetrazolyl) in an AII-induced rabbit aortic ring contraction assay clearly demonstrated the importance of the substitutional position of the carboxyl group. In an in vivo assay, oral administration of benzimidazole-7-carboxylic acids caused long-lasting inhibition of the AII-induced pressor response in rats. The optimum substituent at the 7-position of the benzimidazole ring was found to be a carboxyl or an ester group. The representative compound, 2-butyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid [CV-11194 (I; R1 = 7-CO2H, R2 = 5-tetrazolyl)], inhibited the specific binding of [125I]AII to bovine adrenal cortical membrane with an IC50 value of 5.5 + 10-7 M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11194 (IC50 value, 5.5 + 10-11 M), while the compound had no effect on the contraction induced by norepinephrine or KCl. Orally administered CV-11194 at doses of 0.3-10 mg/kg dose-dependently inhibited the AII-induced pressor response in rats and dogs. CV-11194 at a mg/kg po reduced blood pressure in spontaneously hypertensive rats (SHR). The three-dimensional mol. structure of CV-11194 was determined by x-ray diffraction.

ST nonpeptide angiotensin II receptor antagonist; tetrazolylbiphenylylmethylbutylbenzimidazole antihypertensive angiotensin receptor antagonist; benzimidazole tetrazolylbiphenylylmethylbutyl angiotensin receptor antagonist; structure bioactivity relationship biphenylylmethylbenzimidazole antihypertensive; tetrazolylbiphenylylmethylbenzimidazolecarboxylic acid **crystal** mol structure

IT Receptors
RL: RCT (Reactant); RACT (Reactant or reagent)
(angiotensin II antagonists, N-[(tetrazolylbiphenylyl)methyl]benzimidazole)

IT **Crystal structure**
(of N-[(tetrazolylbiphenylyl)methyl]butylbenzimidazole carboxylic acid)

IT Antihypertensives
(N-[(tetrazolylbiphenylyl)methyl]benzimidazole)

IT Molecular structure-biological activity relationship
(angiotensin-inhibiting, of N-[(tetrazolylbiphenylyl)methyl]benzimidazoles)

IT 638-29-9, Valeroyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation by, of aminobenzoate derivs.)

IT 134-20-3, Methyl 2-aminobenzoate 619-45-4, Methyl 4-aminobenzoate 4518-10-9, Methyl 3-aminobenzoate 5202-89-1, Methyl 2-amino-5-chlorobenzoate 18595-13-6, Methyl 2-amino-6-methylbenzoate 18595-16-9, Methyl 2-amino-5-methylbenzoate
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation of, with valeroyl chloride)

IT 114772-38-2 114772-54-2 124750-51-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-alkylation by, of butylbenzimidazole)

IT 603-85-0, 2-Amino-3-nitrophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(O-methylation of)

IT 18542-63-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclocondensation of, with phenylenediamine)

IT 95-54-5, 1,2-Phenylenediamine, reactions 95-83-0, 4-Chloro-1,2-phenylenediamine 102-51-2, 4-Methoxy-1,2-phenylenediamine
RL: RCT (Reactant); RACT (Reactant or reagent)

(cyclocondensation of, with valeroylimidate)
IT 16554-45-3P, 2-Methoxy-6-nitroaniline
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-acylation of, with valeric anhydride)
IT 5851-44-5P, 2-Butylbenzimidazole
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and N-alkylation of (bromomethyl)biphenyl derivative)
IT 5000-76-0P, 2-Butyl-5-chlorobenzimidazole 127007-39-0P 136285-33-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-alkylation of, by (bromomethyl)biphenyl derivative)
IT 127007-35-6P 136285-49-9P 136285-54-6P 136285-58-0P 136332-68-8P
147330-24-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and N-alkylation of, by (bromomethyl)biphenyl derivs.)
IT 133052-87-6P 133075-99-7P 133085-92-4P 133085-96-8P 133142-54-8P
133142-58-2P 133224-90-5P 135069-70-4P 135069-71-5P 136284-47-4P
136284-48-5P 136284-51-0P 136284-55-4P 136284-56-5P 136284-58-7P
136284-59-8P 136284-60-1P 136284-61-2P 136284-62-3P 136284-65-6P
136284-66-7P 136284-74-7P 136284-78-1P 136285-26-2P 136285-27-3P
136285-28-4P 136285-35-3P 139742-86-2P 147330-16-3P 147330-17-4P
147330-18-5P 147330-19-6P 147330-20-9P 147330-21-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and angiotensin II receptor antagonism by)
IT 79046-81-4DP, benzimidazole analog 79046-96-1DP, benzimidazole analogs
124750-99-8DP, benzimidazole analog
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and angiotensin II receptor antagonism of)
IT 136285-71-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and chlorination of cyclocondensation of, with sodium azide)
IT 135071-03-3P 136285-18-2P 136285-19-3P 136285-20-6P 136285-38-6P
136285-46-6P 136285-51-3P 136285-56-8P 136304-61-5P 136304-62-6P
136304-63-7P 136304-65-9P 136304-66-0P 136304-82-0P 137747-49-0P
147330-23-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclocondensation of, with sodium azide)
IT 136304-60-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and ethanolysis of, ester from)
IT 127007-34-5P 136285-48-8P 136285-53-5P 136285-57-9P 136285-60-4P
136304-94-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and nitration of)
IT 136285-72-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with nucleophiles)
IT 136285-37-5P 136285-45-5P 136285-50-2P 136285-55-7P 136285-59-1P
136285-63-7P 136304-64-8P 139743-06-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reductive cyclization of)
IT 136285-36-4P
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation and reductive cyclization or N-alkylation of, by (bromomethyl)biphenyl derivative)

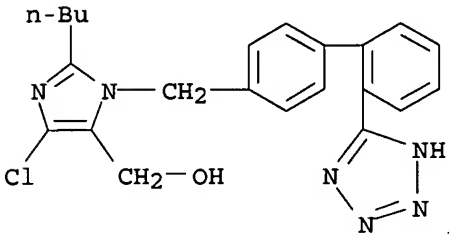
IT 133052-50-3P 147330-22-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and saponification of)

IT 147330-25-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT **124750-99-8DP**, benzimidazole analog
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and angiotensin II receptor antagonism of)

RN 124750-99-8 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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L48 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1993:11760 HCAPLUS
DN 118:11760
ED Entered STN: 10 Jan 1993
TI Direct-compression tablets containing **DUP753**
IN Katdare, Ashok V.; Cunningham, John C.
PA Merck and Co., Inc., USA
SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K031-415
ICS A61K009-20
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 511767	A1	19921104	EP 1992-303526	19920421	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, PT, SE					
	WO 9219228	A1	19921112	WO 1992-US3246	19920421	<--
	W: BG, CS, FI, HU, NO, PL, RO, RU					
	CA 2067307	AA	19921030	CA 1992-2067307	19920427	<--
	AU 9215229	A1	19921105	AU 1992-15229	19920428	<--
	CN 1066184	A	19921118	CN 1992-103205	19920428	<--
	ZA 9203068	A	19921230	ZA 1992-3068	19920428	<--
	JP 06157309	A2	19940603	JP 1992-108255	19920428	<--
	NO 9303806	A	19931022	NO 1993-3806	19931022	<--

PRAI US 1991-692747 A 19910429 <--
WO 1992-US3246 W 19920421 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
EP 511767	ICM	A61K031-415
	ICS	A61K009-20

AB The title tablets comprise **DUP753** 10-45, **microcryst.** cellulose 20-40, lactose 10-30, Mg stearate 0.5-0.9, and pregel starch 35%.

ST **DUP753** tablet direct compression

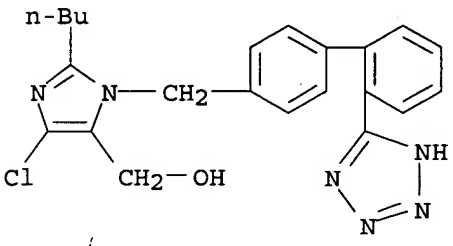
IT Pharmaceutical dosage forms
(tablets, of **DuP753**, by direct compression)

IT **124750-99-8, DuP753**
RL: BIOL (Biological study)
(tableting of, by direct compression)

IT **124750-99-8, DuP753**
RL: BIOL (Biological study)
(tableting of, by direct compression)

RN 124750-99-8 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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L48 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:612716 HCAPLUS
DN 117:212716
ED Entered STN: 28 Nov 1992
TI Preparation of tetrazolylphenylboronic acid intermediates for the synthesis of angiotensin II receptor antagonists
IN Lo, Young S.; Rossano, Lucius T.
PA USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C07D257-02
INCL 548110000
CC 29-4 (Organometallic and Organometalloidal Compounds)
Section cross-reference(s): 1
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5130439	A	19920714	US 1991-793514	19911118 <--

US 5206374	A	19930427	US 1992-911813	19920710	<--
US 5310928	A	19940510	US 1992-911812	19920710	<--
WO 9310106	A1	19930527	WO 1992-US9979	19921118	<--
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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE					
AU 9331792	A1	19930615	AU 1993-31792	19921118	<--
AU 665388	B2	19960104			
EP 643704	A1	19950322	EP 1993-900550	19921118	<--
EP 643704	B1	20030917			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE					
JP 08500323	T2	19960116	JP 1992-509518	19921118	<--
CA 2123900	C	19980714	CA 1992-2123900	19921118	<--
CZ 283954	B6	19980715	CZ 1994-1205	19921118	<--
SK 280887	B6	20000912	SK 1994-579	19921118	<--
AT 250043	E	20031015	AT 1993-900550	19921118	<--
EP 1384717	A2	20040128	EP 2003-18662	19921118	<--
EP 1384717	A3	20040204			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, IE					
ES 2203614	T3	20040416	ES 1993-900550	19921118	<--
FI 9402282	A	19940517	FI 1994-2282	19940517	<--
FI 112945	B1	20040213			
NO 9401857	A	19940718	NO 1994-1857	19940518	<--
NO 307932	B1	20000619			

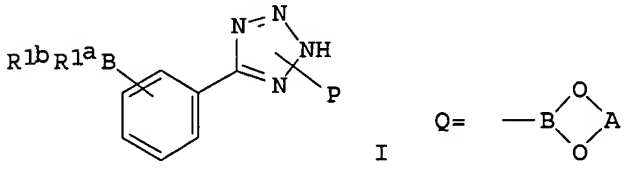
PRAI	US 1991-793514	A3 19911118	<--
	US 1992-911812	A 19920710	<--
	US 1992-911813	A 19920710	<--
	EP 1993-900550	A3 19921118	<--
	WO 1992-US9979	A 19921118	<--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
US 5130439	ICM	C07D257-02	
	INCL	548110000	
US 5130439	NCL	548/110.000	<--
US 5206374	NCL	548/110.000	<--
US 5310928	NCL	548/252.000; 548/250.000; 548/254.000	
	ECLA	C07F005/02C; C07F005/05	<--
EP 1384717	ECLA	C07F005/02C	<--

OS MARPAT 117:212716

GI



AB Title compds. I [P = Ph3C, Me3C, C1-4 alkoxymethyl, MeSCH2, Ph-C1-4-alkoxymethyl, 4-(MeO)C6H4CH2, 2,4,6-Me3C6H2CH2, CH2CH2(SiMe3), tetrahydropyranyl, piperonyl, PhSO2; R1a, R1b = Br, Cl, C1-4 alkoxy, HO; R1aR1bB = Q wherein A = Ph, (CH2)n wherein n = 2-4] are prepared as angiotensin II receptor antagonist intermediates. 5-Phenyltetrazole, Et3N and Ph3CCl were reacted to give 5-phenyl-2-trityltetrazole which was treated with BuLi in **heptane** followed by (Me2CH)3BO3 to give I (P = 2-Ph3C, R1a = R1a = HO).

ST tetrazolylphenylboronate prepn intermediate angiotensin antagonist;

angiotensin receptor antagonist intermediate tetrazolylphenylboronate
IT 11128-99-7, Angiotensin II
RL: RCT (Reactant); RACT (Reactant or reagent)
(antagonists, tetrazolylphenylboronic acid as intermediates for)
IT 6952-59-6, m-Bromobenzonitrile
RL: PROC (Process)
(conversion of, to tetrazole)
IT 143722-27-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and boronation of)
IT 133909-97-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and bromination of)
IT 143722-31-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and conversion to potassium salt)
IT 133909-99-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of)
IT 143722-26-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and lithiation of)
IT 135050-95-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and mesylation of)
IT **114798-26-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of angiotensin II antagonist intermediates)
IT 133051-88-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with imidazolecarboxaldehyde derivative)
IT 87268-78-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with triisopropyl borate)
IT 133910-00-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)
IT **124750-99-8P** 138804-35-0P 143722-29-6P
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of)
IT 143722-30-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for angiotensin II receptor antagonist)
IT 143722-25-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediates for angiotensin II receptor antagonist)
IT 143722-28-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, reduction and reaction with butylchloroimidazolecarboxaldehyde)
IT 76-83-5, Tritylchloride

RL: RCT (Reactant); RACT (Reactant or reagent)
(protection by, of phenyltetrazole)

IT 18039-42-4, 5-Phenyltetrazole
RL: PROC (Process)
(protection of, by trityl chloride)

IT 83857-96-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (bromomethyl)biphenylyltriphenylmethyltetrazole)

IT 1122-91-4, p-Bromobenzaldehyde
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (triphenylmethyl)tetrazolyl boronic acid)

IT 106-38-7, p-Bromotoluene
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (triphenylmethyl)tetrazolylboronic acid)

IT 873-75-6, p-Bromobenzyl alcohol
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with (triphenylmethyl)tetrazolylphenylboronic acid)

IT 26628-22-8, Sodium azide
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with bromobenzonitrile)

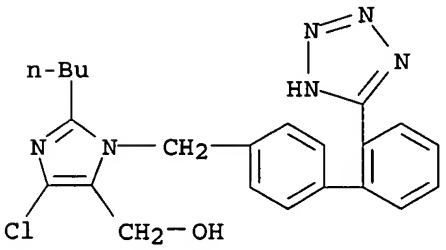
IT 589-15-1, p-Bromobenzyl bromide
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with pentylchloroimidazolecarboxaldehyde)

IT 5419-55-6, Triisopropylborate
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with phenyltitryltetrazole)

IT **114798-26-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of angiotensin II antagonist intermediates)

RN 114798-26-4 HCAPLUS

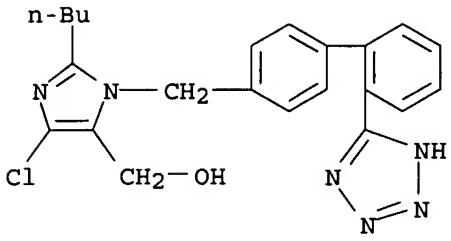
CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- (9CI) (CA INDEX NAME)



IT **124750-99-8P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of)

RN 124750-99-8 HCAPLUS

CN 1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt (9CI) (CA INDEX NAME)



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    FOR DETAILS. <<<

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L69  ANSWER 1 OF 7  WPIX  COPYRIGHT 2005 THE THOMSON CORP on STN
AN   2004-661967 [64]   WPIX
DNC  C2004-236393
TI   New amorphous form of losartan potassium is
     angiotensin II antagonist useful as an antihypertensive agent.
DC   B02
IN   NARASA, R A; NARASA, R B; PARTHASARADHI, R B; RAJI, R R; RATHNAKAR, R K
PA   (HETE-N) HETERO DRUGS LTD
CYC  102
PI   WO 2004076443   A1 20040910 (200464)* EN    8    C07D403-10
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LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
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AU 2003209669 A1 20040917 (200501) C07D403-10

ADT WO 2004076443 A1 WO 2003-IN37 20030225; AU 2003209669 A1 AU 2003-209669 20030225, WO 2003-IN37 20030225

FDT AU 2003209669 A1 Based on WO 2004076443

PRAI WO 2003-IN37 20030225

IC ICM C07D403-10
ICS A61K031-4178

AB WO2004076443 A UPAB: 20041006
NOVELTY - Amorphous form of **losartan potassium** (I) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for preparations of (I).

ACTIVITY - Hypotensive.

MECHANISM OF ACTION - Angiotensin II antagonist.

USE - (I) is useful as an antihypertensive agent.

ADVANTAGE - Amorphous form of (I) has higher bioavailability and has adequate chemical stability upon storage when compared to crystalline form of (I).

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B05-A01A; B07-D09; B07-D13; **B12-M11G**; B14-F02B1

TECH UPTX: 20041006
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises
(a) either dissolving the crystals of (I) in methanol and/or ethanol and vacuum or spray drying the solution thus obtained; or
(b) dissolving the crystals of (I) in a mixture comprising alcohol (methanol or ethanol) and either **ethylacetate** or chloroform and vacuum or spray drying the solution thus obtained.
Preferred Process: The alcohol used in vacuum drying is methanol and in spray drying is ethanol. Preferred Components: (I) is characterized by a **powder** x-ray diffraction pattern.

ABEX UPTX: 20041006
ADMINISTRATION - Administration of (I) is oral. No dosage given.

EXAMPLE - **Losartan potassium** crystals (50 g) were added to the mixture containing methanol (100 ml) and **ethylacetate** (150 ml) and stirred for 1 hour to dissolve. The solution is dried under vacuum at 35-40 degrees C for 18 hours to give amorphous form of **losartan potassium** (42 g).

L69 ANSWER 2 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-604169 [58] WPIX

DNC C2004-218849

TI New alkali earth metal, sodium and potassium salts of losartan used for treatment of hypertension.

DC B03

IN ANTONCIC, L; COPAR, A; HAM, Z; HUSU-KOVACECIC, B; MAROLT, B; SVETE, P

PA (LEKT) LEK PHARM DD

CYC 108

PI WO 2004066997 A2 20040812 (200458)* EN 110 A61K031-4178
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

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KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
US UZ VC VN YU ZA ZM ZW

ADT WO 2004066997 A2 WO 2004-SI1 20040129

PRAI SI 2003-270 20031105; SI 2003-25 20030130;
SI 2003-26 20030130; SI 2003-145 20030612;
SI 2003-157 20030626

IC ICM A61K031-4178
ICS A61P009-12; C07D403-10

AB WO2004066997 A UPAB: 20040910
NOVELTY - Alkali earth metal salts of losartan (I) are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) sodium salt of losartan (II);
(2) potassium salt of losartan in a crystalline form (III) with bound water, characterized by a **powder** X-ray diffraction pattern with peaks at (2 theta) of 13.0, 17.2, 19.7, 20.9, 21.0, 23.2, 23.6, 24.5, 25.0, 26.6, 17.3, 28.2, 29.0, 31.5 deg. ; where the water content is 7-12 weight%;
(3) potassium salt of losartan (IV) (Form X) in a crystalline form, characterized by a **powder** X-ray diffraction pattern with peaks (2 theta) of 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 in 29.2 deg. ;
(4) potassium salt of losartan (V) (Form Y) in a crystalline form, characterized by a **powder** X-ray diffraction pattern with peaks (2 theta) of 6.7, 13.8, 17.4, 19.2, 24.5, 24.8, 25.2 in 28.9 deg. ;
(5) potassium salts of losartan in a crystalline form, which comprises other specified **powder** X-ray diffraction patterns;
(6) alkali or earth alkali metal salts of losartan (VI) in amorphous form, with proviso that the alkali salt of losartan is not potassium salt of losartan;
(7) preparation of alkali and alkali earth metal salts of losartan;
(8) preparation of (II);
(9) purification of losartan which comprises converting losartan into a salt, isolating the salt and converting the isolated salt into losartan;
(10) preparation of (III);
(11) preparation of (IV);
(12) converting (V) or its solvates into (IV) which comprises drying (V) in a vacuum or at normal pressure at at least room temperature;
(13) preparation of (VI);
(14) preparation of an amorphous potassium salt of losartan which comprises drying (III);
(15) industrial scale preparation of potassium salt of losartan in crystalline Form X, and
(16) a composition which comprises a potassium salt of losartan in a crystalline form sensitive to moisture which comprises 25-33% potassium salt of losartan, 55-70 weight% microcrystalline cellulose, 2-10 weight% croscarmellose, and anhydrous silica.
ACTIVITY - Hypotensive.
No biological data is given.
MECHANISM OF ACTION - None given.
USE - Used for the treatment of hypertension (claimed).
Dwg.0/36

FS CPI

FA AB; DCN

MC CPI: B05-A01A; B05-A01B; B07-D09; B07-D13; B12-M11H; B14-F02B

TECH UPTX: 20040910
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of alkali and alkali earth metal salts of losartan which comprises addition of an alcoholate of an alkali or an earth-alkali metal to a

solution of losartan in an alcohol or a mixture comprising alcohol and non-protic solvent, precipitation or crystallization of the obtained salt, and isolation of the obtained precipitated or crystallized salt by filtration or centrifugation.
Preparation of (II) comprises addition of a solution of sodium hydroxide to a solution of losartan until the pH is 9-12, precipitation or crystallization of the obtained salt by the addition of an aprotic solvent; and isolation of the obtained precipitated or crystallized salt by filtration or centrifugation.
Preparation of (III) comprises conversion of the potassium salt of losartan in presence of water.
Preparation of (IV) comprises isolation from methanol or solvent mixture comprising methanol.
Industrial preparation of potassium salt of losartan in crystalline Form X which comprises removing the protecting group from 2-n-butyl-4-chloro-5-hydroxymethyl-1-(2'-triphenylmethyl-2H-tetrazol-5-yl)(1,1'-biphenyl-4-yl)methyl)imidazole, forming a potassium salt with potassium alcoholate, crystallizing and isolating and optionally milling potassium salt of losartan in a crystalline form.
Preparation of (VI) comprises suspending losartan in water, adding an aqueous solution of alkali metal or alkali earth hydroxide or alcoholate at above 0degreesC until the pH is least 3, freezing the obtained solution of salt of losartan and lyophilizing the obtained frozen solution.
Preferred Process: Purification of losartan comprises uses alkali or alkali earth metal salts of losartan. The water used in the preparation of (I) is present as moisture or in mixture with one or more solvents which do not mix with water or poorly mix with water;,and the preparation of (III) includes the preparation of a concentrated aqueous solution of potassium salt of losartan (where the mass of water is 0.4-1.2 times the mass of losartan), and isolation of a potassium salt of losartan in a crystalline form by drying and milling.
Preparation of (III) also comprises isolation from solvent which is methanol or solvent mixture comprising methanol. The alkali salt is a sodium salt of losartan and alkali earth metal salt is a calcium salt or magnesium salt for the preparation of (IV) and the last step of the process comprises lyophilization of frozen aqueous solution of alkali or earth alkali salt of losartan.
Preferred Components: The potassium salt of losartan comprises more than 50% of particles having a diameter of 5-500 (preferably below 100) mum.

ABEX UPTX: 20040910
ADMINISTRATION - Administration of (I) is peroral or parental. No dosage is given.

EXAMPLE - To losartan (40.81 g) in isopropanol (235 ml), a solution of sodium hydroxide (5.5 g) in water (5.7 ml) was added at 38-40degreesC to a pH of 12 over half an hour. 35 ml of azeotropic mixture isopropanol/water were removed by distillation, n-**heptane** (140 ml) was added and the reaction mixture was stirred at room temperature to form a white solid. The resulting suspension was diluted with n-**heptane** (55 ml), filtered, washed with n-**heptane** (110 ml) and dried in vacuo at 50degreesC to yield sodium salt of losartan (110 ml).

L69 ANSWER 3 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-389201 [36] WPIX
DNC C2004-145716
TI New crystalline form III of **losartan potassium**, useful as angiotensin II receptor inhibitor for the treatment of e.g. hypertension and congestive heart failure.
DC B03 C02
IN ESWARAIAH, S; KOPPERA, R R; REDDY, M S; REDDY, V V

PA (REDD-N) REDDY'S LAB LTD
CYC 1
PI US 2004097568 A1 20040520 (200436)* 11 A61K031-4178
ADT US 2004097568 A1 US 2003-629316 20030729
PRAI IN 2002-CH568 20020729
IC ICM A61K031-4178
ICS C07D403-02
AB US2004097568 A UPAB: 20040720
NOVELTY - A crystalline form III of **losartan potassium** (A1) is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) A composition (c1) comprising (A1) as a solid (where at least 80, preferably at least 90, especially at least 95, particularly at least 99 weight% is its crystalline form III);
(2) A pharmaceutical or veterinary composition (c2) comprises (A1) and carrier or diluent; and
(3) Preparation of (A1) in the form of crystalline form III.
ACTIVITY - Hypotensive; Cardiovascular-Gen.
MECHANISM OF ACTION - Angiotensin II receptor inhibitor.
USE - Crystalline form III of **losartan potassium** (A1) is useful in pharmaceutical and veterinary formulations for the treatment of hypertension and congestive heart failure.
ADVANTAGE - The solid **losartan potassium** is free of crystalline form I and II of **losartan potassium.** At least 1 (preferably 5) % of the solid **losartan potassium** is not its crystalline form III. (A1) is active as an angiotensin II (AII) blocker. The composition is safe and non-toxic.
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: B05-A01A; B07-D09; B07-D13; B12-M11H; B14-F01B; B14-F02B1; C05-A01A; C07-D09; C07-D13; C12-M11H; C14-F01B; C14-F02B1
TECH UPTX: 20040608
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: Composition (c2) further comprises at least one excipient, lubricant, disintegrant, coloring agent, anti-hygroscopic agent, binder, pH adjusting agent, flavoring agent, or aromatic agent. In (c2), (A1) is present in an amount of 0.01 - 99.99 (preferably 1 - 95, especially 2 - 20, particularly 1 - 10) wt.%.
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (A1) in the form of crystalline form III involving:
(1) providing a potassium salt of losartan as a solution in a first alcohol solvent;
(2) cooling the solution to cause separation of a solid mass; and
(3) isolating the solid mass.
The method further involves removing at least a portion of the first alcoholic solvent before the cooling step; reacting trityl losartan with potassium hydroxide to obtain the starting potassium salt of losartan; removing at least a portion of the second alcoholic solvent and combining the reaction mixture with water and a water-immiscible solvent to form a two-phase liquid system; separating the layers of the two-phase liquid system, isolating the aqueous layer and reducing the amount of water present in it; combining the reduced aqueous layer with a second water-immiscible solvent capable of forming an azeotropic mixture with water and heating the second water-immiscible solvent to reflux with removal of the distillate to reduce the amount of the water; adding a lower alkanol to provide a starting solution of the potassium salt of losartan in the first alcoholic solvent; drying the separating mass at 30 - 100 degrees C; removing at least a portion of the first alcoholic solvent; cooling the reaction mass to cause separation of a solid mass and

isolating the separated mass.
The reacting step involves contacting the trityl losartan with the potassium hydroxide in a second alcoholic solvent and heating the second alcoholic solvent to reflux until the reaction is complete. The cooling step is carried out at 0 - 50 degrees C. The isolating step is filtration of the solid mass. The step 1) involves dissolving a crystalline form I of **potassium losartan** in the aromatic solvent and adding the lower alkanol. The crystalline form I **losartan potassium** is combined with the aromatic solvent at 50 - 80 degrees C.
Preferred Compound: (A1) is confirmed by X-ray **powder** diffraction pattern which is expressed in 2 theta angles and obtained with a copper K X-radiation source as given in the specification; differential scanning colorimetry thermogram exhibiting a significant endo peak at 264 degreesC as given in the specification; infrared spectrum exhibiting significant bands as given in the specification. (A1) has a melting point of 254 - 260 degreesC.
Preferred Components: The carrier or diluent is a solid or a liquid. The first alcoholic solvent is the lower alkanol (preferably 1-4C alkanol, especially group A, particularly methanol). The group A is selected from methanol, ethanol, isopropanol, n-butanol, iso-butanol and/or tert-butanol. The alcoholic solvent is a mixture of lower alkanol and at least one aromatic solvent (preferably **toluene**). The trityl losartan and the potassium hydroxide are reacted at the molar ratio of 0.5:1.5 - 1.5:0.5. The second alcoholic solvent is different from the first alcoholic solvent and is selected from group A. The second water-immiscible solvent is different than the first water-immiscible solvent. The second water-immiscible solvent, the first water-immiscible solvent and at least one aromatic solvent are selected from **benzene**, **xylene**, **toluene** and/or ethyl **benzene.**

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The carrier or diluent is selected from derivatized cellulosic material, starch and/or polyhydroxylated alcohol.

ABEX UPTX: 20040608
ADMINISTRATION - Composition (c2) is administered in a solid dosage form (e.g. tablet) oral, topical, systemic, injectable, transdermal, implantable, inhalable, transmucosal or dermal; or in the form of **powder**, tablet, dragees, capsules, oil, cream, solution, emulsion or suspension (all claimed).

EXAMPLE - Trityl losartan (125 g) was placed in a mixture of an aqueous solution of potassium hydroxide (11 g in 125 ml of water) and methanol (1250 ml) and refluxed until the reaction was substantially complete. Solvent was distilled off the solution under vacuum, and water (375 ml) was added to the residual mass, which was then stirred for the 30 minutes, filtered and washed with water (150 ml). The obtained filtrate was washed with **toluene** (2 x 110 ml, and the aqueous layer was separated from the resulting bi-phasic mixture. Water was distilled off the aqueous layer, and any remaining water traces were removed under reflux as an azetrope formed by addition of **toluene** (350 ml).
Methanol (100 ml) and carbon (5.5 g) were added, and the residue stirred for 30 minutes until clear. Following filtration, washing and distillation, the reaction mass was cooled to 20-25 degreesC to separate the solid mass. The solid was filtered, washed with methanol (50 ml) and dried at 80-90 degrees C to obtain crystalline Form III **losartan Potassium** (75 g; 86.5%).

L69 ANSWER 4 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 2004-375582 [35] WPIX
DNC C2004-141203
TI Increasing the flowability of **losartan potassium powder** useful for treating hypertension, comprises reslurrying the losartan **powder** in a solvent.
DC B03 B07
IN **KOR, I; LIFSHITZ, I; SHABAT, S**
PA (KORI-I) KOR I; (LIFS-I) LIFSHITZ I; (SHAB-I) SHABAT S; (TEVA-N) **TEVA PHARM IND LTD**; (TEVA-N) **TEVA PHARM USA INC**
CYC 107
PI WO 2004035049 A1 20040429 (200435)* EN 19 A61K031-4178
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004171843 A1 20040902 (200458) C07D403-02
AU 2003284262 A1 20040504 (200467) A61K031-4178
EP 1471908 A1 20041103 (200472) EN A61K031-4178
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2004035049 A1 WO 2003-US32885 20031017; US 2004171843 A1 Provisional US 2002-419450P 20021017, Provisional US 2002-426072P 20021112, Provisional US 2002-426461P 20021114, Provisional US 2002-431450P 20021204, Provisional US 2002-431809P 20021209, US 2003-688697 20031017; AU 2003284262 A1 AU 2003-284262 20031017; EP 1471908 A1 EP 2003-776442 20031017, WO 2003-US32885 20031017
FDT AU 2003284262 A1 Based on WO 2004035049; EP 1471908 A1 Based on WO 2004035049
PRAI US 2002-431809P 20021209; US 2002-419450P 20021017;
US 2002-426072P 20021112; US 2002-426461P 20021114;
US 2002-431450P 20021204; US 2003-688697 20031017
IC ICM A61K031-4178; C07D403-02
ICS **A61K009-14**; A61K031-41
AB WO2004035049 A UPAB: 20040603
NOVELTY - Increasing the flowability of **losartan potassium powder** initially having a Hausner ratio of at least 1.45 comprises reslurrying the losartan **powder** in a solvent, where the solvent is hydrocarbon, alkyl ether and/or alkyl ester.
ACTIVITY - Hypotensive.
MECHANISM OF ACTION - AT1 angiotensin II receptor antagonist.
USE - For treating hypertension.
ADVANTAGE - The isolated and dried **losartan potassium powder** has a Hausner ratio of less than 1.45 (preferably less than 1.3), so that the **powder** has improved flowability and hence the problems occurs with handling and processing during milling and formulating are reduced.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B07-D09; B07-D13; **B12-M11G**; B14-F02B; B14-F02B1
TECH UPTX: 20040603
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The reslurrying is carried out at the boiling point of the solvent. The method additionally involves isolating and drying **losartan potassium** after the reslurry to form a **powder** and milling the isolated and dried **losartan potassium.**
Preparation of the **losartan potassium** involves

neutralizing losartan free acid with a potassium base (e.g. potassium hydroxide) in the presence of a protic solvent (preferably an alcohol, especially isopropanol).
Preferred Components: The solvent is **hexane**, **heptane**, **cyclohexane**, **methylcyclohexane**, **benzene**, **toluene**, **xylene**, **ethyl acetate**, **propyl acetate**, **butyl acetate**, **diethyl ether** or **dibutyl ether**.

ABEX UPTX: 20040603
ADMINISTRATION - Dosage of the **losartan potassium powder** is 10 - 100 (preferably 25 - 50) mg and administered by oral, buccal, parenteral (such as subcutaneous, intramuscular and intravenous), rectal, inhalant and ophthalmic route.

EXAMPLE - Dry **losartan potassium** (50 g) was reslurried in **cyclohexane** (200 ml) at 80degreesC for 4 hours. The suspension was filtered and dried at 50 - 60degreesC for 10 hours to form the **losartan potassium powder** having Hausner ratio of 1.3 - 1.35 which shows free flowing property.

L69 ANSWER 5 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-903636 [82] WPIX
DNC C2003-257065
TI Production of losartan or its salt useful as anti hypertensive agent involves acid catalyzed cleavage of triarylmethyl from triarylmethyl-substituted losartan derivative in a liquid ketone.
DC B03
IN DOLITZKY, B; KAFTANOV, J; NISNEVICH, G; RUCHMAN, I
PA (DOLI-I) DOLITZKY B; (TEVA-N) **TEVA PHARM IND LTD**; (TEVA-N) **TEVA PHARM USA INC**
CYC 104
PI WO 2003093262 A2 20031113 (200382)* EN 14 C07D401-10
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004034077 A1 20040219 (200414) C07D403-02
AU 2003228767 A1 20031117 (200442) C07D401-10
EP 1474417 A2 20041110 (200473) EN C07D401-10
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2003093262 A2 WO 2003-US13369 20030429; US 2004034077 A1 Provisional US 2002-376322P 20020429, US 2003-426612 20030429; AU 2003228767 A1 AU 2003-228767 20030429; EP 1474417 A2 EP 2003-726536 20030429, WO 2003-US13369 20030429
FDT AU 2003228767 A1 Based on WO 2003093262; EP 1474417 A2 Based on WO 2003093262
PRAI US 2002-376322P 20020429; US 2003-426612 20030429
IC ICM C07D401-10; C07D403-02
AB WO2003093262 A UPAB: 20031223
NOVELTY - Preparation of losartan or its salts involves contacting tetrazole derivative and an acid in a diluent; basifying the diluent; evaporating liquid ketone, by leaving residue; precipitating a triarylmethyl alcohol compound followed by separation; acidifying the residue followed by precipitation and separation.
DETAILED DESCRIPTION - Preparation (M1) of losartan or its salts (preferably potassium salt) involves:

(a) contacting tetrazole derivative of formula (II) and an acid in a diluent (preferably liquid ketone) to convert the compound to losartan;
(b) basifying the diluent;
(c) evaporating liquid ketone, by leaving residue;
(d) precipitating a triarylmethyl alcohol of formula (III);
(e) separating (III) from the residue; and
(f) acidifying the residue followed by precipitation and separation.
R1, R2, R'1, R'2, R''1 and R''2 = alkyl or alkenyl (both optionally substituted by at least one of halo, OH or lower alkoxy), nitro, cyano, vinyl, styryl, -COR3, CO2R3, -OR3, -SR3, -SO2R3, -NR3R4, -NCO2R3, -OCO2R3, H or halo;
R3 and R4 = H, lower alkyl, aralkyl or (hetero)aryl; or
R1+R2, R'1+R'2, R''1+R''2 when on adjacent positions = optionally substituted carbocyclic or heterocyclic ring.
preferably: when the R1, R2, R'1, R'2, R''1 and R''2 occupy two adjacent positions, then R1+R2, R'1+R'2, R''1+R''2 is -CHCHCHCH-.
An INDEPENDENT CLAIM is included for preparation (M2) of **losartan potassium** comprising:
(a) contacting losartan with potassium in a diluent comprising isopropyl alcohol, butyl alcohol or isobutyl alcohol;
(b) precipitating **losartan potassium** from the diluent; and
(c) separating the precipitated losartan from the diluent.
ACTIVITY - Hypotensive.
MECHANISM OF ACTION - Angiotensin (AT1) receptor antagonist.
USE - For the preparation of losartan or its salts (preferably potassium salt) (claimed), which is useful as anti-hypertensive agent.
ADVANTAGE - The process provides the losartan with high yield of at least 91% and purity of at least 97%.
Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B07-D09; B07-D13; B14-F02B1
TECH UPTX: 20031223

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The diluent is basified to a pH of 10 - 14 using a base (preferably sodium hydroxide or potassium hydroxide, especially potassium hydroxide). (M1) further involves
(1) converting the separated triarylmethyl alcohol to a reagent for protecting a tetrazole; and
(2) using the reagent to prepare a compound of formula (II).
The step (2) involves protecting 5-phenyltetrazole with the reagent to give a 2-(triarylmethyl)-5-phenyltetrazole (i); converting (i) to a 2-(2'-triarylmethyl-2'H-tetrazol-5'yl)phenylboronic acid compound (IV); and converting (IV) to (II). Conversion of (IV) involves either:
(a) contacting (IV) with 2-n-butyl-4-chloro-5-hydroxymethyl-1-parabromobenzyl-1H-imidazole under Suzuki conditions to obtain 2-n-butyl-4-chloro-1-((2'-(2-triarylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl)-1H-imidazole-5-carboxaldehyde compound (V); and converting (V) to (IV) using a reducing agent; or
(b) contacting (IV) with para-bromotoluene under Suzuki conditions to obtain 5-(4'-methyl-1,1'-biphenyl-2-yl)-2-triarylmethyl-2H-tetrazole (VI); contacting (VI) with a brominating agent to obtain 5-(4'-bromomethyl-1,1'-biphenyl-2-yl)-2-triarylmethyl-2H-tetrazole (VII); contacting (VII) with 2-n-butyl-4-chloro-1H-imidazole-5-carboxaldehyde to obtain a 2-n-butyl-4-chloro-1-((2' -(2-triarylmethyl-2H-tetrazol-5-yl)-1,1'-biphenyl-4-yl)methyl)-1H - imidazole-5-carboxaldehyde (VIII); and converting (VIII) to (II) with a reducing agent.
The residue is acidified to a pH of 2 - 4 (preferably 3.5 - 3.6) using hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid,

hydrobromic acid and formic acid (preferably hydrochloric acid and sulfuric acid). (M1) further involves extracting the residue with a water immiscible organic solvent after precipitating the triarylmethanol and before separating the losartan from the residue; and recovering losartan from the water immiscible organic solvent.
The losartan produced by (M1) is further converted into **losartan potassium** by (M2).
Preferred Method (M2): The losartan is contacted with potassium (0.9 - 1.1) molar equivalent with respect to losartan. (M2) further involves evaporating a portion of the isopropyl alcohol diluent after contacting and before precipitating. The losartan is contacted with potassium by adding a solution of potassium ions to a heterogeneous mixture of losartan and the diluent. The solution of potassium ions is prepared by adding a potassium ion source (selected from potassium hydroxide, potassium isopropoxide, potassium butoxide and potassium isobutoxide) to the diluent. The diluent is heated before precipitating **losartan potassium.**
Preferred Components: The diluent is a mixture of the liquid ketone (50 - 90%) and water (10 - 50%). The liquid ketone is acetone, methyl ethyl ketone or methyl isobutyl ketone (preferably acetone).

ABEX UPTX: 20031223
SPECIFIC COMPOUNDS - 7 Compounds are specifically claimed as (II), e.g. 2-butyl-4-chloro-1-((2'-(2-triphenylmethyl-2H-tetrazol-5-yl)(1,1'-biphenyl)-4-yl)methyl)-1H-imidazole-5-methanol.

ADMINISTRATION - The **losartan potassium** is administered in a dosage of 25 - 100 mg/day by oral route.

EXAMPLE - Aqueous hydrochloric acid (39.1 ml) was added to a suspension of trityl losartan (26 g) in acetone (150 ml) at room temperature. The reaction mixture was stirred for 5 hours. A solution of potassium hydroxide (11 g) in water (100 ml) was slowly added and acetone was evaporated under reduced pressure. The reaction mixture was worked up to give triphenyl methanol. **Ethyl acetate** (100 ml) was added to the aqueous filtrate and the biphasic mixture was vigorously stirred and acidified to pH 3.5 - 3.6 and worked up to give losartan (yield: 91%) with purity of 97.68%. A solution of potassium hydroxide (0.305 g) and isopropyl alcohol (15 ml) was slowly added to a suspension of the losartan (2 g) in isopropyl alcohol (25 ml). The reaction mixture was stirred for 2 hours at room temperature. The mixture was filtered, concentrated for 12 hours at room temperature and then worked up to give **losartan potassium** (1.85 g; yield 85%) and purity of 99.74%.

DEFINITIONS - Preferred Definitions:
R1, R2, R'1, R'2, R1 and R2 = H or -OCH3.

L69 ANSWER 6 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-569039 [53] WPIX
DNC C2003-153457
TI New amorphous and crystalline forms of **losartan potassium** useful for treating hypertension.
DC B03
IN DOLITZKY, B Z; KAFTANOV, J; NISNEVICH, G; RUKHMAN, I; WEIZEL, S; NISNEVICH, G A; WIZEL, S
PA (TEVA-N) **TEVA PHARM IND LTD**; (TEVA-N) **TEVA PHARM IND INC**; (TEVA-N) **TEVA PHARM USA INC**
CYC 103
PI WO 2003048135 A1 20030612 (200353)* EN 23 C07D257-04
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU

MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
ZA ZM ZW

US 2004006237 A1 20040108 (200404) A61K031-4178
AU 2002360386 A1 20030617 (200419) C07D257-04
EP 1458693 A1 20040922 (200462) EN C07D257-04
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC
MK NL PT RO SE SI SK TR
NO 2004002434 A 20040611 (200512) C07D257-04
ES 2234451 T1 20050701 (200545) C07D257-04
MX 2004004657 A1 20040901 (200553) C07D257-00

ADT WO 2003048135 A1 WO 2002-US36550 20021113; US 2004006237 A1 Provisional US 2001-333034P 20011114, Provisional US 2002-401278P 20020805, US 2002-293820 20021113; AU 2002360386 A1 AU 2002-360386 20021113; EP 1458693 A1 EP 2002-795637 20021113, WO 2002-US36550 20021113; NO 2004002434 A WO 2002-US36550 20021113, NO 2004-2434 20040611; ES 2234451 T1 EP 2002-795637 20021113; MX 2004004657 A1 WO 2002-US36550 20021113, MX 2004-4657 20040514

FDT AU 2002360386 A1 Based on WO 2003048135; EP 1458693 A1 Based on WO 2003048135; ES 2234451 T1 Based on EP 1458693; MX 2004004657 A1 Based on WO 2003048135

PRAI US 2002-401278P 20020805; US 2001-333034P 20011114;
US 2002-293820 20021113

IC ICM A61K031-4178; C07D257-00; C07D257-04
ICS A61K031-41; A61K031-411; C07D403-02; C30B000-00000

AB WO2003048135 A UPAB: 20030820
NOVELTY - Amorphous **losartan potassium** is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) **losartan potassium** in crystalline hydrate form;
(2) **losartan potassium** form IV and it's solvates;
(3) **losartan potassium** form V and it's solvates;
(4) **losartan potassium** in a crystalline form; and
(5) preparation of the amorphous and crystalline forms of **losartan potassium.**
ACTIVITY - Hypotensive.
MECHANISM OF ACTION - Competitive AT1 angiotensin II receptor antagonist.
USE - For treating hypertension (claimed).
ADVANTAGE - The **losartan potassium** forms have improved bulk handling and dissolution properties. The amorphous **losartan potassium** contains less than 10% crystalline **losartan potassium** and is substantially free of crystalline **losartan potassium.**
Dwg.0/9

FS CPI
FA AB; DCN
MC CPI: B05-A01A; B07-D09; B07-D13; B12-M11H; B14-F02B1
TECH UPTX: 20030820
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compounds: The **losartan potassium** is in the form of amorphous (A), hydrated crystalline form (B), crystalline form IV (C) and crystalline form V (D) or their solvates.
Preparation:
(1) Preparation (P1) of (A) involves dissolving **losartan potassium** in a solvent (s1) to form a solution, and removing (s1) from the solution;
(2) Preparation (P2) of (B) involves exposing amorphous **losartan**

potassium or **losartan potassium** form I to an atmosphere having a relative humidity greater than 60%;
(3) Preparation (P3) of (C) involves:
(a) mixing a solution of **losartan potassium** in (s2) having a boiling point of at most 135 degrees C;
(b) adding methylene chloride to the solution to form suspension; and
(c) isolating **losartan potassium** form IV.
(4) Preparation (P4) of (D) involves:
(a) mixing a solution of **losartan potassium** in (s2);
(b) adding hexene to form a mixture; and
(c) isolating **losartan potassium** form V.
(5) Preparation (P5) of **losartan potassium** form II involves mixing a solution of **losartan potassium** in a solvent (s2) having a capacity to solubilize **losartan potassium** at room temperature at a concentration of 0.1 g/ml of solvent, adding the solution to **xylene** to form a mixture, evaporating (s2), and isolating **losartan potassium** form II;
(6) Preparation (P6) of **losartan potassium** form I involves mixing a solution of **losartan potassium** in a first solvent having a boiling point of at most 135 degrees C to form a solution, reducing the temperature of the solution, and isolating **losartan potassium** form I;
(7) Preparation (P7) of **losartan potassium** form I involves heating **losartan potassium** form III at least 50, preferably 100 degrees C.
In (P1), the solvent is removed by lyophilization or by distillation. The distillation is performed at a pressure of at most 300 mm Hg (preferably 2 -100 mm Hg). The exposing step is performed for 1-5 days. (P3) and (P4) additionally involves reduction of the temperature of the suspension or the mixture (preferably 2-3 degrees C) and maintaining for a holding time (preferably 1-3 hours). In (P5) the temperature of the solvent is reduced to about 2-3 degrees C and the mixture is maintained at this temperature for 1-3 hours. In (P5), a slurry is produced by reducing the temperature of the solution. (P6) additionally involves after the reduction step, addition of a second solvent to form a mixture after reducing the temperature of the first solvent to form a precipitate.
Preferred Components: (s1) is an aqueous solvent (preferably water) or 1-6C alcohol (preferably methanol). (B) is tetrahydrate **losartan potassium** form III; and has at least one characteristic of form III. (B) has water content of 12-16, preferably 14%, and the relative humidity of greater than 80%. The solvate is an ethanolate. (C) is confirmed by a differential scanning calorimetric thermogram and differential scanning calorimetric thermogram as given in the specification. (s2) is a 1-6C alcohol (preferably ethanol). The first solvent is a 1-6C alcohol (preferably ethanol or isopropanol). The second solvent is **ethyl acetate**, **toluene**, acetone, methylethyl ketone, methylene chloride, acetonitrile, dimethyl carbonate or **hexane.**

ABEX UPTX: 20030820

ADMINISTRATION - The oral dosage form of (A), (B), (C) or (D) is administered in the form of capsule or tablet (claimed). The dosage of losartan forms are 10-100 (preferably 25-50) mg and administered orally, buccally, parenterally (including subcutaneously, intramuscularly or intravenously), rectally, by inhalation or ophthalmically.

EXAMPLE - **Losartan potassium** (1 g) was stirred in water (2 ml) in a round bottom flask until it dissolved. The solution was then transferred to a heavy walled lyophilization tray. The lyophilizer was cooled to below freezing to -5 degrees C. The lyophilizer was

evacuated and maintained under vacuum (0.01 mm Hg) for 2 hours. The residue was submitted for **powder** X-ray analysis, to produce amorphous **losartan potassium** which produced a featureless diffractogram with a broad peak centered at 22 degree 2theta.

L69 ANSWER 7 OF 7 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-112143 [10] WPIX
DNC C2003-028768
TI New method for the preparation of crystalline form I of **losartan potassium**, useful in the treatment of hypertension, comprises treating losartan acid or trityl losartan with potassium hydroxide in an alcohol and an anti-solvent.
DC B03
IN HANDA, V K; RAMASHANKAR, ; REDDY RAVINDER, V; SIVAKUMARAN, M; RAMASHANKAR, A P L; RAMASHANKAR, H; REDDY, R V; SIVAKUMARAN, M S
PA (AURO-N) AUROBINDO PHARMA LTD
CYC 97
PI WO 2002094816 A1 20021128 (200310)* EN 9 C07D403-10
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
EP 1294712 A1 20030326 (200323) EN C07D403-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
SK 2003000072 A3 20031201 (200404) C07D403-10
JP 2004520446 W 20040708 (200445) 24 C07D403-10
AU 2002222498 A1 20021203 (200452) C07D403-10
ADT WO 2002094816 A1 WO 2001-IN205 20011120; EP 1294712 A1 EP 2001-274254 20011120, WO 2001-IN205 20011120; SK 2003000072 A3 WO 2001-IN205 20011120, SK 2003-72 20011120; JP 2004520446 W WO 2001-IN205 20011120, JP 2002-591489 20011120; AU 2002222498 A1 AU 2002-222498 20011120
FDT EP 1294712 A1 Based on WO 2002094816; SK 2003000072 A3 Based on WO 2002094816; JP 2004520446 W Based on WO 2002094816; AU 2002222498 A1 Based on WO 2002094816
PRAI IN 2001-CH403 20010518
IC ICM C07D403-10
AB WO 200294816 A UPAB: 20040826
NOVELTY - New method for the preparation of crystalline form of **losartan potassium** comprises:

(A) treating an losartan acid or trityl losartan with potassium hydroxide in an alcohol; and

(B) concentrating under reduced pressure to remove alcohol and adding an anti-solvent.

DETAILED DESCRIPTION - New method for the preparation of crystalline form of **losartan potassium** comprises:

(1) treating 2-n-butyl-4-chloro-5-hydroxymethyl-1-((2'-((2H-tetrazole-5-yl)biphenyl-4-yl)methyl)imidazole or 2-n-butyl-4-chloro-5-hydroxymethyl-1-((2'-((triphenylmethyl)tetrazole-5-yl)biphenyl-4-yl)methyl)imidazole with potassium hydroxide (1 mole equivalent) in an alcohol; and

(2) concentrating under reduced pressure to remove alcohol and adding an anti-solvent.

ACTIVITY - Hypotensive; Nephrotropic.

MECHANISM OF ACTION - Inhibitor of the action of octapeptide hormone angiotensin II.

USE - For the preparation of crystalline form I of **losartan potassium** useful in the treatment of hypertension e.g. angiotensin induced hypertension. Also, **losartan potassium** is

useful in combination with non-steroidal anti-inflammatory drug for the prevention of renal failure.

ADVANTAGE - The **losartan potassium** polymorph form I can be prepared in one pot without isolating the free losartan acid and requires no feeding, which results in increased efficiency and lower production cost. The method does not require expensive separation techniques including extraction or isolation of losartan free acid. When trityl losartan is used as the starting material, the method can be carried out under anhydrous condition. The method thus avoids elaborate azeotropic distillation for water removal.

Dwg.0/2

FS CPI

FA AB; DCN

MC CPI: B05-A01A; B07-D09; B07-D13; B10-A15; B10-E04D; B10-F02; B10-G02; B10-J02; B14-F02B1; B14-N10

TECH UPTX: 20030211

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: An in situ de-protection is carried out to produce **losartan potassium.**

ABEX UPTX: 20030211

SPECIFIC COMPOUNDS - Methanol, ethanol, propanol and butanol are specifically claimed as the alcohol.

Acetone, **ethyl acetate**, acetonitrile and **toluene** are specifically claimed as the anti-solvent.

EXAMPLE - To a suspension of 2-n-butyl-4-chloro-5-hydroxymethyl-1-((2'-((2H-tetrazole-5-yl)biphenyl-4-yl)methyl)imidazole (losartan acid) (5 g) in methanol (25 ml), potassium hydroxide **powder** (0.75 g) was added and mass stirred at ambient temperature to obtain clear solution. The resulting solution was filtered and the clarified solution was concentrated to remove most of methanol at 45-50 degrees C under reduced pressure. **Ethyl acetate** (25 ml) was added and distillation continued to distil most of the methanol/**ethyl acetate** mixture. The residue was diluted with ethyl acetone (25 ml) and contents cooled to 20-25 degrees C for 10 minutes and product filtered under nitrogen atmosphere and washed with **ethyl acetate** (5 ml). The resulting product was dried under reduced pressure to yield **losartan potassium** form I (4.95 g; 91%).

=> d his

(FILE 'HOME' ENTERED AT 09:03:03 ON 20 AUG 2005)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:03:09 ON 20 AUG 2005
E LOSARTAN/CN
L1 1 S E3
L2 1 S E4,E6
L3 22 S 114798-26-4/CRN
L4 6 S L3 AND K/ELS
L5 6 S L2,L4
L6 16 S L3 NOT L5
L7 9 S L6 NOT MXS/CI
L8 7 S L6 NOT L7

FILE 'HCAPLUS' ENTERED AT 09:06:29 ON 20 AUG 2005
L9 327 S L5
L10 833 S LOSARTAN(A)(K OR POTASSIUM OR MONOPOTASSIUM OR MONO POTASSIUM
L11 2199 S L1

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L12          20 S L1 (L)(K OR POTASSIUM OR MONOPOTASSIUM OR MONO POTASSIUM)
L13         853 S L9,L10,L12
                E LIFSHITZ/AU
L14          18 S E34-E37
                E KOR/AU
L15           4 S E10
                E SHABAT/AU
L16           3 S E13,E16
                E TEVA/PA,CS
L17         322 S E3-E83
L18           3 S L13 AND L14-L17
L19       50920 S CYCLO HEXANE OR METHYL CYCLOHEXANE OR METHYL CYCLO HEXANE OR
L20      655900 S HEXANE OR HEPTANE OR CYCLOHEXANE OR METHYLCYCLOHEXANE OR BENZ
L21          14 S L13 AND L19,L20
L22           2 S L18 AND L21

     FILE 'REGISTRY' ENTERED AT 09:16:40 ON 20 AUG 2005
L23          12 S 60-29-7 OR 71-43-2 OR 108-87-2 OR 108-88-3 OR 109-60-4 OR 110
L24       16229 S (60-29-7 OR 71-43-2 OR 108-87-2 OR 108-88-3 OR 109-60-4 OR 11
L25         227 S L24 NOT ((PMS OR MXS OR IDS OR MNS OR AYS OR TIS)/CI OR LABEL

     FILE 'HCAPLUS' ENTERED AT 09:19:11 ON 20 AUG 2005
L26          10 S L23 AND L13
L27           0 S L25 AND L13
L28          15 S L21,L22,L26
L29           9 S L28 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L30          36 S L13 AND (?POWD? OR ?CRYS?)
L31           7 S L30 AND L29
L32          76 S L13 (L) (PREP+NT OR PROC+NT)/RL
L33           6 S L32 AND L29
L34           5 S L32 AND L31
L35           8 S L18,L22,L33,L34
                E POWDER/CT
                E E42+ALL
L36           0 S E4 AND L13
L37          25 S L30 AND (PY<=2002 OR PRY<=2002 OR AY<=2002)
L38           6 S L37 AND L35
L39           8 S L35,L38
L40          19 S L37 NOT L39
                SEL DN AN 2 7 12 L40
L41           3 S L40 AND E1-E9
L42          11 S L39,L41
L43          16 S L40 NOT L42
                SEL DN AN 13
L44           1 S L43 AND E10-E12
L45           3 S L43 AND ((CRYSTAL MORPHOLOGY OR CRYSTAL STRUCTURE)/CT OR DUP7
L46          14 S L42,L45 AND L9-L22,L26-L45
L47          11 S L46 AND LOSARTAN
L48          14 S L46,L47

     FILE 'HCAPLUS' ENTERED AT 09:29:28 ON 20 AUG 2005

     FILE 'WPIX' ENTERED AT 09:30:48 ON 20 AUG 2005
L49          53 S L10/BI,ABEX
                E LOSARTAN/CN
L50           4 S E3-E7
                SEL SDCN
                EDIT /SDCN /DCN
L51         217 S E1-E5
L52         228 S L49,L51
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L53          40 S L52 AND (L19/BI,ABEX OR L20/BI,ABEX)
L54          10 S (HEXANE OR HEPTANE OR CYCLOHEXANE OR METHYLCYCLOHEXANE OR BEN
L55           2 S (PROPYL-ACETATE OR DIETHYL-ETHER OR DIBUTYL-ETHER)/CN
                E DIBUTYL ETHER/CN
                E DIBUTYLETHER/CN
                E DIBUTYL-ETHER/CN
                E N-DIBUTYL-ETHER/CN
L56          12 S L54,L55
                SEL SDCN
                EDIT /SDCN /DCN
L57        7053 S E1-E12
L58           4 S L52 AND L57
                E R01146+ALL/DCN
L59       13994 S E1 OR (1146 0204 OR 1056 RO 1135 OR 0862 OR 0306 OR 0913 OR 1
L60           3 S L52 AND L59
L61          40 S L53,L58,L60
L62           6 S L61 AND ?POWD?/BI,ABEX
L63           2 S L61 AND R036/M0,M1,M2,M3,M4,M5,M6
L64           2 S L61 AND (B12-M11G OR C12-M11G)/MC
L65           2 S L61 AND A61K009-14/IPC
L66           3 S L61 AND TEVA?/PA
L67           1 S L61 AND (LIFSHITZ ? OR KOR ? OR SHABAT ?)/AU
L68           8 S L62-L67
L69           7 S L68 NOT PRESSURE/TI

     FILE 'WPIX' ENTERED AT 09:40:50 ON 20 AUG 2005

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